TAMPERE UNIVERSITY OF TECHNOLOGY

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SIDE-EFFECT OF CHEMOTHERAPY ON LIVER IN LYMPHOMA PATIENTS STUDIED BY STANDARD UPTAKE VALUE

Master's Thesis

Examiner:
Professor Hannu Eskola

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ABSTRACT

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Keywords: Diffuse Large B-cell Lymphoma, 18 F-FDG PET/CT, SUV, Chemotherapy, Liver.

The aim of this thesis study is to ascertain if there are changes in F-18 FDG uptake in the liver after chemotherapy R-CHOP in patients having diffuse large B-cell non-Hodgkin's lymphoma. PET using 18 F-FDG is used to detect enhanced glycolysis in cancer cells and has proven to be valuable in diagnosis, staging and assessing response to therapy in a multitude of malignant disorder. PET/CT images of 19 patients both male and female, aged between 48 to 80 years was analyzed in the present study. PET/CT scan of the patients were taken one week before, one week after, one month after and four months after chemotherapy. The images in all these cases were analyzed for changes in F-18 FDG uptake in liver before the treatment with R-CHOP and in different period after treatment. The changes were quantified by means of standard uptake value. The changes in standard uptake value were also compared with changes in liver function test before and one month after chemotherapy.

The present study demonstrates there are changes in alanine aminotransferase, alkaline phosphatase and mean 18 F-FDG uptake in liver by R-CHOP chemotherapy in patients with diffuse large B-cell Non-Hodgkin's lymphoma. However, the decrease in ALT and AFOS value was not significant one month after chemotherapy.

Preface

This Master of science thesis has been carried out in the oncology department of the Tampere University Hospital. I would like to thank Professor Hannu Eskola for giving me the opportunity to work, learn and guide me on throughout my thesis. I would also like to thank Dr. Xingchen Wu for her invaluable support. My special gratitude to Pasi korkola and Veikko Suihko and Hannu Pertovara for valuable help in laboratory work. I would also thank my friends and family for their support and encouragement.

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18F-FDG	: 18 Fluorine Fluoro deoxy Glucose
3D	: Three Dimensional
AFOS	: Alkaline Phosphatase
AIDS	: Acquired Immune Deficiency Syndrome.
ALT	: Alanine Aminotransferase
CT	: Computed Tomography
DLBCL	: Diffuse Large B cell Lymphoma
DNA	: Deoxyribonucleic Acid
EUCAN	: European Network of Cancer Registries
FAD	: Fludarabine, doxorubicin, dexamethasone
FMD	: Fludarabine, Mitoxantrone and dexamethasone
GE	: General Electric
Kbq	: Kilobecquerel
Mbq	: Megabecquerel
MRI	: Magnetic Resonance Imaging
NHL	: Non-Hodgkin's Lymphoma
PET	: Positron Emission Tomography
PET/CT	: Positron Emission Tomography/Computed Tomography
R-CHOP	:Rituximab Cyclophosphamide Doxorubicin Hydrochloride Vincristine Prednisolone
REAL	: Revised European American classification of the lymphoid neoplasm
RF	: Radio frequency
ROI	: Region of Interest
SUV	: Standard Uptake Value
SUVmax	: Standard Uptake Value Maximum
SUVmean	: Standard Uptake Value minimum
WHO	: World Health Organization

1 Introduction

The role of imaging modalities has been pivotal to the study and diagnosis of different diseases. In cancer studies, it plays a vital role. Especially in cases of aggressive cancers such as diffuse large B cell lymphoma where early detection, diagnosis and treatment can be lifesaving. Positron tomography coupled with Computed tomography has been useful in this scenario, which enables both the metabolic and anatomical studies to take place. Furthermore, providing functional and anatomical images to facilitate better diagnosis. Diffuse Large B cell Lymphoma (DLBCL) is the most common type of lymphoma and accounts for 30-40% of all non-Hodgkin's lymphoma cases [10]. DLBCL is a very aggressive type of Non-Hodgkin's lymphoma and can arise from either the lymph nodes or organs such as GI tract, skin, breast, bone, testes and thyroid. Due to its nature it can proliferate very fast in different part of the body so early identification and treatment is imperative.

Among various treatment techniques available to mitigate DLBCL chemotherapy is used widely and frequently. Administering the R-CHOP regimen to eradicate tumor cell is a very common practice. Apart from treating the tissue intended the medication has side effects on the whole body. In our study, we assess the effect of chemotherapy regimen on liver by measuring the standard uptake value before chemotherapy is administered to the patient and subsequently after each cycle of medication administered. Radiopharmaceutical is administered into the body which contains glucose and it circulates throughout the body. Tumor cells are known to consume more glucose than normal tissue to fuel their high rate of growth and division. So, as more glucose is absorbed by tumor compared to normal tissue more positrons are emitted from tumorous part of the body and consequently detected by positron scanner. The uptake of the radiopharmaceutical is different in normal and cancerous tissue, which can be measured via semi quantitative analysis called standard uptake value (SUV). In SUV injected dose, the patient's weight and time after injection are all taken into account.

Fusion PET/CT using 18F-fluorodeoxy glucose 18F-FDG is an imaging technique that displays the 18F-FDG uptake throughout the body. Tumour cells are more active than normal cells and consume more glucose in our case 18 F FDG to fuel their growth and division. As more glucose in consumed more 18 F-FDG is phosphorylated in the tumorous region and consequently more positrons are emitted. The positrons are detected by the detectors in positron scanner. Areas with more activity are seen brighter compared to areas with lower activity. The variance of the two

measured activities depends on the uptake by the tissue. This difference in the uptake of glucose helps to separate tumorous and normal tissue. PET/CT is used not only for detection of cancer, but also to monitor the individual response to therapy. Changes in FDG accumulation in different parts of the body after treatment are seen as a useful marker to evaluate the effectiveness and response to therapy.

Accumulation of FDG in tissue can be measured by calculating the amount of the dose given and the weight of the patient. However, our interest is not on the overall accumulation of FDG in some region, but rather on the relative uptake of FDG on the region of interest compared to other parts of the body [13]. The SUV mean obtained from this process is considered reliable if the region of interest can be defined accurately [13]. The accurate selection of a region of interest was greatly assisted by implementing fusion imaging, which involved both computed tomography (CT) and PET images. With the aid of CT images, proper region of interest could be segmented and the same region of interest was applied to the PET image to get reliable SUV mean, SUV max values. PET/CT scan of the patients were taken one week before chemotherapy, one week after, one month after and three to four months after chemotherapy [16]. The images in all these cases were analyzed for changes in F-18 FDG uptake in the liver before the treatment with R-CHOP and in different period after treatment.

This thesis study was undertaken to evaluate the changes in F-18 FDG uptake in the liver after chemotherapy RCHOP on patients having Non- Hodgkin's lymphoma. The study is carried out by analyzing PET/CT scan before chemotherapy and one week, one month and four months after chemotherapy. The analysis also compares to liver based enzyme alanine aminotransferase and alkaline phosphatase value before and one month after treatment.

2 Background

Lymphoma is a cancer associated with the lymphatic system and lymph nodes. Lymphoma can be broadly classified as Hodgkin's and non-Hodgkin's lymphoma. The prevalence of Hodgkin's and non-Hodgkin's lymphoma accounts for 3.2% of total cancer cases with a mortality rate of 2.8% as per a study conducted by the International Agency for cancer research in 2012 [1]. The survival rate of patients with Hodgkin's lymphoma is comparatively greater than patients with non-Hodgkin's lymphoma. National Cancer Institute, USA predicts non-Hodgkin's and Hodgkin's lymphoma will account for total of 3.2% and 0.2% of all cancer related death, respectively, and estimates 70,800 new non-Hodgkin's lymphoma and 9,190 Hodgkin's lymphoma cases in the USA the following year [2].

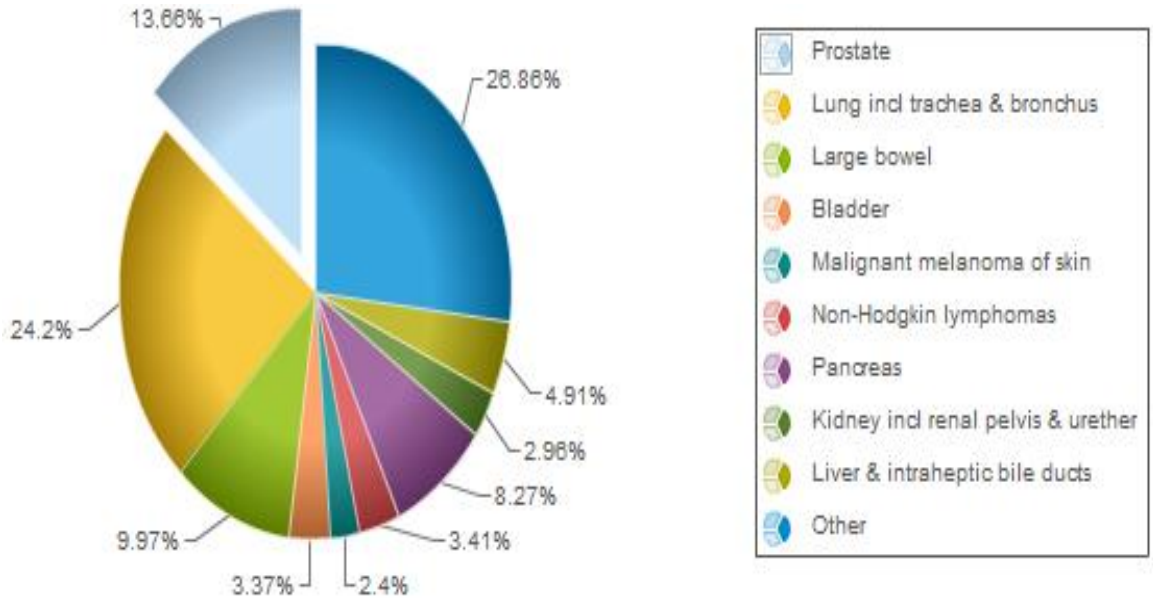

Figure 2-1 Mortality of men by different cancer types. Adapted from [47]
Figure 2.1 shows mortality of men in Finland by different cancer in 2012.

In non-Hodgkin's lymphoma lymphocytes T cell and B cells divide abnormally. Lymphoma generally involves B cell lymphocytes, which divide without control [3]

[24]. Some lymphomas are slow growing, whereas some grow fast and aggressively, which require prompt attention in regards to diagnosis and treatment Both Hodgkin's and non-Hodgkin's lymphoma are similar in character and can be differentiated by biopsy. Presence of Reed-Sternberg cell in the cancer indicates the cancer is Hodgkin's lymphoma. The occurrence of Hodgkin's lymphoma has been in decline as compared to non-Hodgkin's lymphoma, which has been on an increasing trend in the USA [4].

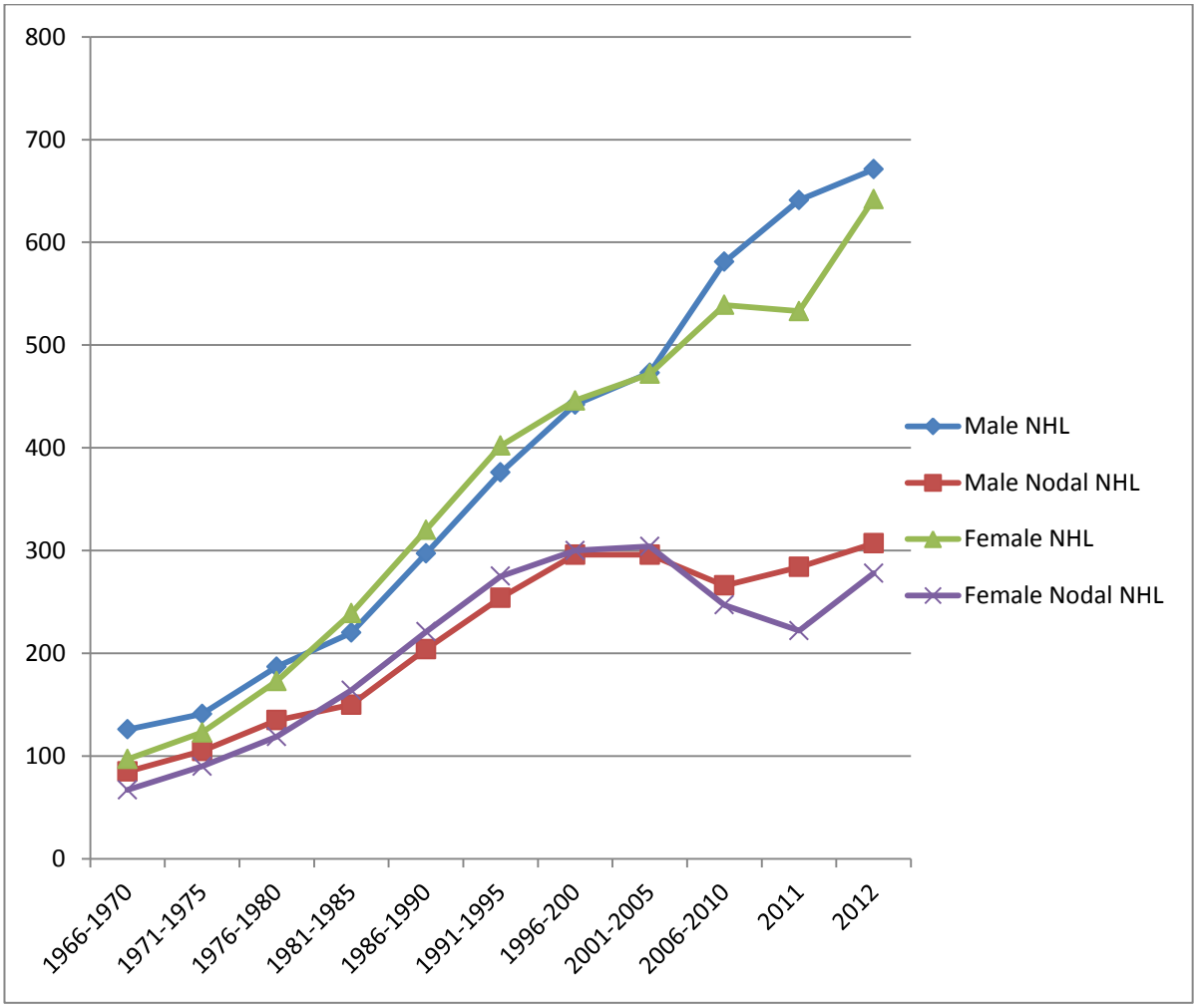

Figure 2-1 NHL new cases Finland from 1966 to 2012.
Mean annual number of new cancer cases of Male and female with NHL and Nodal NHL from 1966 to 2012. Data adapted from [50].

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Lymphomas are very different and diverse type of cancer and the exact cause of occurrence of this cancer are still unknown. The DNA mutation inherited from parent's increase the chance of some cancer, but lymphoma is not the type of cancer which is inherited [6] [24]. As cells divide a new set of chromosomes are developed and this

process is not perfect, and the divided cell may have different DNA genes of the parent cell. Cancer may develop due to DNA mutation of tumor suppressor genes.

2.1 Diffuse Large B cell lymphoma

It is the most common type of lymphoma and accounts for 30-40% of all non-Hodgkin's lymphoma cases [10]. DLBCL is an aggressive type of NHL and develops from B cell in the lymphatic system. There are three different types of DLBCL.

2.1.1 T-cell/histiocyte-rich large B cell Lymphoma

T-cell/histiocyte-rich large B cell lymphoma can affect people of any age, but it is most prevalent in men over 50 years of age [15] [24]. This type of lymphoma accounts for less than 10% of total DLBCL cases. As the type name suggests T-cell, histiocytic and B cells are all involved in this form of DLBCL. It causes swelling of liver, spleen, lymph nodes and fever. Symptoms include swelling of the abdomen and discomfort. R-CHOP is used in the treatment of this lymphoma and in cases of relapsing high dose chemotherapy regimen or even stem cell transplant is used.

2.1.2 Primary mediastinal large B cell lymphoma

Primary mediastinal large B cell lymphoma can occur to people of any age group, but it is most common in 25 - 40 age groups. It is more common in women than men. It develops in mediastinum in the chest. The mass of this cancer puts pressure on lungs, gut, supervene cava. This pressure leads to persistent cough, breathlessness, dizziness, headache, swelling of the neck and face which are the symptoms associated with primary mediastinal large B cell lymphoma [15] [25]. R-CHOP is used in the treatment of this lymphoma. High dose chemotherapy regimen or even stem cell transplant is used in cases of relapse.

2.1.3 Intravascular Large B cell Lymphoma

Intravascular Large B cell Lymphoma is an extremely rare type of DLBCL. It affects people over 65 years of age. In this type of DLBCL malignant lymphocytes are found within small blood vessels as a result any body part can be affected but its occurrence in lymph node and bone marrow is very rare. It also affects the nervous system as a result, people have symptoms such as dizziness, weakness, loss of balance

change in vision, difficulty to speak and understand [15]. Treatment in patients with Intravascular Large B cell Lymphoma is generally high dose chemotherapy where it is applicable

2.2 REAL classification

The classification of different type of lymphoma has been a tricky and challenging issue for a long period of time. For very long clinicians and scientists were classifying different type of lymphoma on the basis of REAL classification. Recently REAL classification has been revised under the initiative of WHO. This revised classification broadly classifies lymphomas on the basis of morphology and cell lineage [7].

- B-cell neoplasms
- T-cell/natural killer cell neoplasm
- Hodgkin's lymphoma

Lymphoma and lymphoid leukemias are both included in this classification as in many lymphoid neoplasms, both circulating and solid phases are present in many of the cases [7]. B cell neoplasms, T cell neoplasms and Hodgkin's lymphoma have been categorized into different types based on immunological and genetic techniques which help improve understanding and treatment of various subtypes of lymphoma. As per data provided by cancer research UK between 2004-2011 it has been seen that almost half i.e. 48% of all non-Hodgkin's lymphoma cases accounted for was a particular subtype of B cell neoplasm, more specifically Diffuse large cell B lymphoma. So, the incidence rate for diffuse large cell B lymphoma was 9 and 8 for every 100,000 men and women respectively [8]. In our research, we are only focusing on this particular subtype of Non-Hodgkin's lymphoma. It grows fast and aggressively so prompt diagnosis and treatment can be life saving

2.3 Symptoms

Lymphomas have very common symptoms such as painless swelling in neck, armpit or groin. Some people find the area of swelling aches. Apart from swelling, weight loss, night sweats, fever, feeling fatigued, difficulty in recovering from infections, itching of skin all over the body, difficulty in recovering from infections are symptoms associated with lymphomas [12]. Symptoms of diffuse large B cell

lymphoma generally depend on the site and period of development. Enlarged nodes in chest in patients with DLBCL can cause breathlessness or cough. Diarrhea, abdominal pain and bleeding in case of DLBCL in stomach [28].

2.4 Staging

After confirming the presence of lymphoma by physical examination, biopsies, blood test, imaging techniques, the cancer is staged into four groups according to the spread of cancer in the body. Ann Arbour system is used for staging lymphoma, which consists of four stages represented in roman numerals, followed by an alphabet which signifies affected organ. As per Ann Arbour staging of lymphoma cancer, it can be staged as:

Table 1 Lymphoma Stages

Stage	Spread of cancer in body
Stage I	Lymphoma has affected only one lymph node area or lymphoid organ.
Stage II	Lymphoma has affected two or more groups of lymph nodes or lymphoid organs either above the diaphragm or below it but not on the either side.
Stage III	Lymphoma has affected lymph nodes above and below the diaphragm
Stage IV	Lymphoma has spread into nearby organs, bone marrow, brain, liver, spinal cord.

During staging of lymphoma letters such as E or S or ES is used, for example IIIES indicates lymphoma is present on either side of the diaphragm and has spread into nearby organs (E) and spleen (S).

2.5 Previous Work

There have been numerous studies carried out to see the changes in SUV of liver and mediastinum due to R-CHOP and ACVBP chemotherapy in patients with non-hodgkins lymphoma. Many authors have assumed liver SUV uptake to be normal and as a reference in their study such that 18 F-FDG accumulation on lesion greater than the liver at a certain point is considered abnormal [25]. It has been reported that SUV values of liver and mediastinum for normal cancer free patient are stable over time [46]. Studies by chiracvalloti et al., Ceriani et al., kaya et al. have all conducted studies to see changes in liver SUV due to chemotherapy. However, none of these studies have been able to ascertain the change is due to chemotherapy. There have been numerous studies on liver and mediastinum, but no study has able to address if there are any metabolic change in liver due to R-CHOP chemotherapy in patients with non hodgkins lymphoma.

2.6 Aim

Many studies have focused on the liver and mediastinum to see changes in SUV before and after chemotherapy. In this thesis study, including the changes in liver SUV we also take into account the changes in liver based enzymes such as alanine aminotransferase and alkaline phosphatase. These are the enzymes most abundantly found in the liver and can give an indication of the health of the liver. The abnormal level of an enzyme in the organ can be an indication of it being under stress or disease. In our study, we aim to include liver function test along with liver SUV values before and after chemotherapy. In this way we will be able to better understand and determine if there are changes in liver due to chemotherapy. So the incorporation of liver function test with liver standard value uptake to analyse the changes due to R-CHOP chemotherapy will be the aim of this study.

2.7 Imaging modality for diagnosis

Identification of lymphoma is followed by monitoring the prevalence and spread of cancer around the body. The spread of cancer into various areas determine the stage of cancer. The staging processes categories the spread of the cancer in the body. Various imaging techniques and biopsies can be performed to determine the stage of cancer and its spread throughout the body. Imaging modalities such as CT scan, MRI, PET scan, PET-CT, PET/MRI and ultrasonography are used to determine the occurrence and spread of cancer in the body and the area affected by it. Imaging is generally followed by a biopsy. Biopsies are performed to confirm lymphoma. In cases where radiation can be an issue, especially for pregnant women, non-radiation based imaging technique such as MRI or ultrasonography can be used. In biopsy a small sample of bone, blood and bone marrow is extracted from the hipbone or breastbone and the sample is then analyzed to look for signs of cancer.

2.7.1 Magnetic resonance Imaging

Magnetic Resonance Imaging (MRI) is an image acquisition technique developed in 1970s [40]. It uses a magnetic field and high energy radio frequency wave to obtain high quality images. MRI is a highly preferred imaging technique for soft tissue and in cases where ionization can be an issue. It is generally non-invasive, but in some cases the contrast enhancing agents can be administered for obtaining better contrast [41]. MRI machine consists of strong magnetic field and radio frequency wave generator.

The patient is kept inside the machine and the magnetic field switched on and radio pulse is generated. As the body is placed in a strong magnetic field the protons in the body line up to one axis. The alignment of protons in the body creates a magnetic vector along the axis of MRI. A radio wave is applied that causes hydrogen nuclei is dependent on the element and the field strength. The magnetic field is not uniform and varies from head to toe and by altering the local magnetic field the different slices of the body will resonate with different frequency. This creates the different parts of the body to resonate in different frequencies. As the RF source is switched off the magnetic vectors come back to their original state and in the process create signal which are received by the detector [42]. This signal is then used to create a magnetic resonance image.

Magnetic resonance takes longer acquisition time and involves variable protocols compared to PET/CT [39]. Studies have shown whole body MRI to be as effective as PET/CT in staging, localizing tumor. Whole body MRI has several advantages over PET/CT as it gives better contrast, soft tissue images, does not involve ionizing radiation and higher spatial resolution [39].

2.7.2 Positron Emission Tomography (PET)

PET instrument consists of detectors which detect 511 Kev positrons emitted from the radiopharmaceutical. Of the detected positrons only collinear positrons, which strike in a pair are registered. The registered positrons are then used to form images using an iterative expectation maximization algorithm. PET imaging provides resolution of 4-5 mm compared to 15 mm during its inception [14]. Many cancers, including lymphomas metabolize glucose at an abnormally high rate, which forms the basis of cancer imaging by 18F-FDG-PET. Cancer cells have accelerated growth as compared to normal tissue and to sustain such growth it has high metabolic activity. As the 18 F-FDG glucose is injected into the body, it is absorbed significantly high in the tumor cells as compared to normal cells. So, as more 18F-FDG is absorbed from the region, it emits more photons after positron annihilation with an electron.

Various radiopharmaceuticals have been in use in nuclear imaging, but the most common PET pharmaceutical used is Fluorine-18 (FDG). This radio pharmaceutical shows cellular glucose metabolism in the body. Many subtypes of lymphoma, including diffuse large cell B lymphoma, high grade follicular lymphoma, anaplastic large cell lymphoma and Burkett's lymphoma demonstrate high glucose uptake [9].

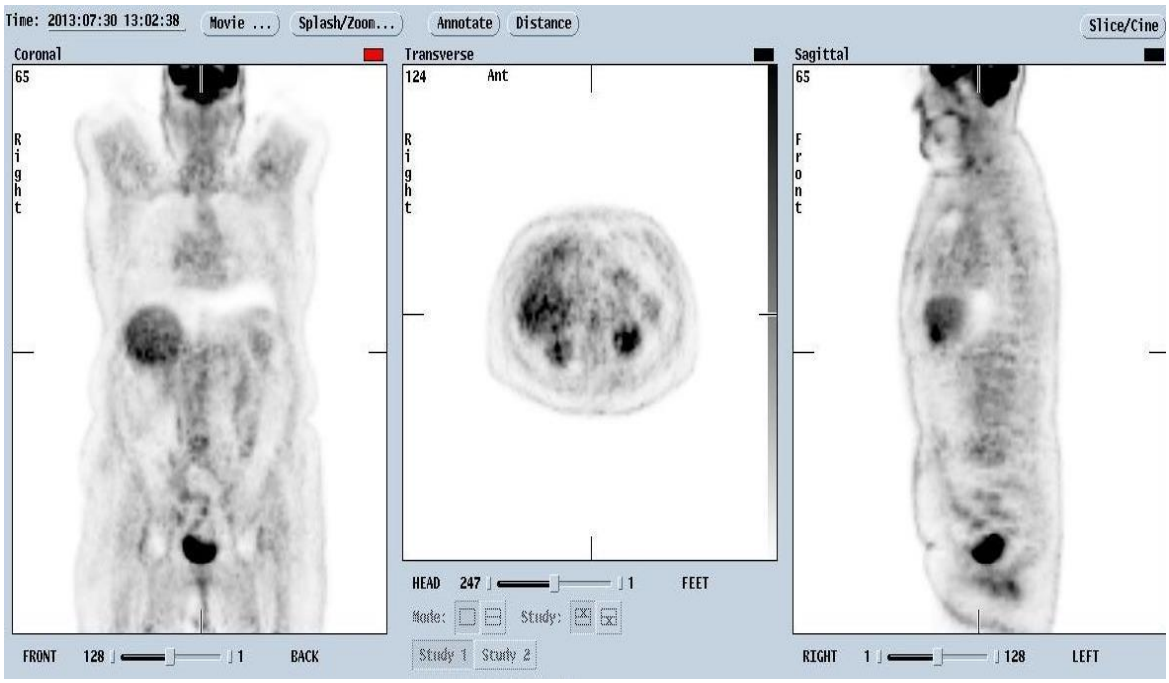

Figure 2-2-2 PET scan.

Coronal, Transverse and sagittal view of the patient under PET/CT examination. The figure above shows PET images which are used for segmentation to obtain standard uptake value.

18 F-FDG is phosphorylated to 18F-FDG-6-phosphate in the tumor cells that cannot be further metabolized. The patient is subjected to fasting for 4-6 hours prior to scan and is instructed to avoid any strenuous physical activity before and after the radiopharmaceutical has been injected to avoid its physiological muscle uptake. FDG dose of 370 Mbq is injected into the patient [16]. The result can be assessed visually by observing low, moderate or high level of activity. Visual inspection depends from one observer to other results in high inter observer variability while assessing the degree of malignancy. So, the tumor assessment needed to be standardized which was done with a semi quantitative assessment using standard uptake value. The SUV is based on the assumption that FDG is distributed evenly throughout the body, but as normal and tumor cells have a different uptake level they can be differentiated which helps in localizing and determining malignancy of tumors [16].

FDG PET has been shown to be superior in specificity, sensitivity and accuracy as compared to CT in the staging of Hodgkin's disease and non-Hodgkin's lymphoma by as much as 85-98% [17]. SUV value obtained is also related to degree of malignancy and can also be used as biomarker. Study by Hutchings M et al. has shown that different histopathological subtype of Hodgkin's disease showed varying FDG uptake value. Another study further strengthened the case where grade III follicular lymphoma had higher FDG uptake than grade I or II [18]. FDG uptake in indolent lymphoma as compared to aggressive lymphoma is low [16]. The superiority of FDG-PET lies in its ability to detect metabolic changes in a malignant tissue before anatomical changes take place [16]. However, some type of low grade lymphomas (small lymphatic, nodal and extra nodal marginal zone, cutaneous T-cell, peripheral T-cell, primary duodenal follicular) show no or very low FDG uptake [19].

Lack of detailed anatomical feature in FDG/PET hinders precise tumor sites. Localizing tumors is important for effective treatment of the lymphoma. Physiological uptake of FDG is high in the GI tract, urinary tract, brain, muscle, brown fat, thymus, salivary gland and lack of accurate anatomical detail in FDG-PET can be a huge problem when localizing tumor and differentiating these physiological uptake with tumor uptake [16]. As we discussed several factors of PET studies can make interpretation of result in accurate and challenging.

2.7.3 Computed Tomography (CT)

Computed tomography is X-ray based imaging device which creates cross sectional images of any part of the body. The device is coupled with high energy electromagnetic source, detectors and powerful computer which work in sync to create high resolution images with great anatomical details. The conventional X-ray system

produces two dimensional data which are only useful in certain cases and does not give a complete picture of the imaged object. Computed tomography on the other hand, provides a complete image of the imaged object and we can select required slice to view body structure of interest.

Computed tomography has evolved a lot with time. Before CT was invented patient had to go through various radiographic examinations that included chest radiography, isotope scans, intravenous pyelography and various other test. Introduction of CT was a breakthrough in non-invasive imaging. Since its inception CT has been widely used in the field of staging of malignant lymphoma. Further advancement in computed tomography i.e. increase in speed in resolution has made it more valuable. Greater speed of image retrieval implies less motion and respiratory induces artifact [33], as a result lymph node smaller than 5 mm could be seen in whole body scan [31] [32].

Modern CT devices are coupled with multiple detectors [29] and in 90's spiral CT was introduced which further improved Computed tomography. CT is commonly used for staging lymphoma because of its availability and also due to cost, as it is relatively cost effective. CT produces excellent anatomical details of tissue and is pivotal in the early staging in lymphoma. Even though CT is used for initial staging it still has a lot of drawbacks that needs to be addressed. Unreliable in the detection of bone marrow disease, poor contrast of the lesion with surrounding tissue and its inability to detect pathological changes, makes use of computed tomography alone questionable [30]. So, the use of CT alone in restaging of malignant lymphoma may not be accurate. Use of positron emission tomography with computed tomography has been very effective in staging and restaging of cancer. CT provides good anatomical details and positron emission tomography provides functional or metabolic details. Both of the images than can be used together for better understanding, diagnosis and treatment of disease. Despite all the facts CT is still useful in staging of lymphoma, but it alone cannot be totally relied on in restaging phase [30].

2.7.4 Fusion Imaging FDG PET/CT

2-deoxy-2-Flourine-18fluoro-D glucose is widely tested and used radiopharmaceutical in positron emission tomography. Diagnosis, staging and treatment of cancer needs to be accurate and on time. 18F-FDG can be valuable in therapeutic management of patients with cancer. It provides valuable functional information regarding tumor. Anatomical imaging modalities show changes after there has been a change in the tissue, whereas functional imaging technique like 18F-FDG PET can

show an area of tumor before any anatomical changes. 18F-FDG is used in staging and restaging and is found to be more sensitive and specific for certain kind of cancers [26]. It has a half-life of 109.8 minutes, which makes it ideal for PET/CT scan [27]. FDG is glucose based radiopharmaceutical, it is not specific to any cancer, but will be accumulated in areas with higher metabolism, such as some muscles, nerves, inflammation, tumor, etc. PET scanning is usually done 60 minutes after the injection which allows adequate time for 18-F-FDG to get absorbed and accumulated.

While radiology mainly shows morphology nuclear techniques exhibit pathophysiology. So, the combination of both of these techniques can yield an image which is superior in quality and information when compared to using these modalities alone which is the feature of PET/CT fusion imaging. Along with a PET scanner CT scanner is also attached to the same device which retrieves images of the patient in slices around neck, chest, abdomen and pelvis. PET and CT scan the patient one after the other and do not work simultaneously. Then the images from both PET and CT are then combined to form a new image which shows distinctly if there is the presence of cancer and its precise location. Fusion imaging enables us to obtain images having both the anatomical and functional information; moreover attenuation in PET can be corrected by information from CT data [16].

Fusion imaging has proven to be very effective in initial staging, monitoring the effect of therapy as well as detection of recurrence. Studies have shown accuracy of FDG-PET over CT in restaging of malignant lymphoma. B cell lymphoma, follicular lymphoma, mantle lymphoma is well visualized in routine staging and restaging [34] [35]. As high quality anatomical and functional images are present the examiner is more informed and is able to take highly accurate decisions as compared to either of the imaging modalities being used alone. The availability of anatomical information as well in form of CT slices makes it more convenient for the examiner to detect tumor sites. As PET images have problem with misinterpretation of physiological uptake the availability of anatomical information will significantly reduce false localization of disease. The advantage of correcting attenuation correction using CT data gives PET/CT fusion imaging an edge over other imaging modalities. However, in case of attenuation correction factors such as contrast agent, beam hardening, motion of patients can affect SUV values so images without attenuation correction should be included in evaluation [16] [20].

CT images can be used for attenuation correction in PET emission data which is highly advantageous, as it reduces significant scanning time by 30 minutes or less [30]. According Kwee et al. this approach also provides low noise attenuation correction factors compared to PET transmission measurement when external radiation source is used. Problems arise when a CT contrast agent is used. Physiological motions and CT beam hardening effect due to metallic implant can result in alteration of the appearance of SUV lesion. So use of both attenuation corrected and uncorrected image should be

used to avoid false diagnosis and misinterpretation [36] [37]. Studies by Schaefer NG et al. has shown that PET/CT scan without contrast agent is sufficient for staging patient with Hodgkin's Disease and aggressive Non-Hodgkin's Lymphoma.

2.8 Standard Uptake value

PET/CT is not only used for detection of cancer, but also for monitoring the individual response to therapy. Changes in FDG accumulation in different parts of the body after treatment are seen as a useful marker to evaluate the effectiveness and response to therapy. Accumulation of FDG in tissue can be measured by calculating the amount of the dose given and the weight of the patient. However, our interest is not on the overall accumulation of FDG in some region of interest but rather on the relative uptake of FDG on the region compared to other parts of the body [13]. SUV interpretation can be greatly affected by blood glucose level, so blood glucose level should be in check during PET/CT scan [49]. Study by Paquet N. has shown stable SUV in cancer free patients over time [46].

(Standard Uptake Value) $SUV = \frac{r}{a/w}$

Where,

r: Radioactivity concentration in ROI [kBq/ml]

a: Amount of Injected FDG [KBq]

w: Patients weight.

Reconstruction of PET image is followed by analysis. During the analysis region of interest, i.e. liver in this case was chosen in the transverse plane on the entire length of the liver. The SUV mean obtained from this process is considered reliable if the region of interest can be defined accurately [13]. The accurate selection of a region of interest was greatly aided by implementing fusion imaging, which involved both computed tomography (CT) and PET images. With the aid of CT images proper region of interest could be selected and the same region of interest was applied to the PET image to get reliable SUV mean, SUV max values. There can also be issues with partial volume effect for small dimension objects.

2.9 Biopsy

Biopsy refers to a sample of tissue of interest taken out of the body for closer examination. A biopsy is generally performed after it can be determined that the tissue of interest is not in a normal state. The extracted sample is then further subjected to another mode of tests and analysis to further diagnose a disease. A biopsy is generally done after imaging of the area of tissue as imaging technique such as x-ray cannot exactly differentiate cancerous and non-cancerous tissue [43]. Various forms of biopsy are performed to make a cancer diagnosis. Bone marrow biopsy, needle biopsy, endoscopic biopsy, skin biopsy and surgical biopsy.

Bone marrow biopsy is performed when diagnosis related to a variety of blood problem is needed. It is generally performed in conditions such as lymphoma, leukemia and multiple myeloma. A long needle is used to extract bone marrow samples from back or other bones where bone marrow is present. Local anesthesia is administered during this procedure. In cases relating to lymphoma core needle biopsy is considered safe and accurate, study by Nguyen et al suggest [44] [45]. The study also recommends an excisional biopsy for suspicious lymphoma.

In endoscopic biopsy extraction tools are mounted on the endoscopic tube which are inserted in the body. Doctors gather visual information regarding the location of the tissue of interest and sample is extracted. Needle biopsy is generally performed when the tumor can be felt from the surface of skin such as lymph nodes or breast lumps. Skin biopsy is performed for skin conditions. Surgical biopsy is performed when above mentioned methods are not applicable and surgery is performed to extract sample or entire tissue which looks abnormal.

2.10 Chemotherapy

Various treatment techniques have been devised which are employed alone or in combination with each other for most effective treatment of the Non-Hodgkin's lymphoma. Generally a team of doctors from different specialty team up to provide the best treatment possible using chemotherapy, radiotherapy, immunotherapy, surgery or even stem cell transplantation. The use of any one of the mentioned techniques or combinations of these techniques varies from patient to patient according to their medical condition. Some patient have indolent lymphoma, which is not harming the organ or its surrounding organs in such case careful and periodic examination of the

patient is done and treatment only begins when the patient shows symptoms tests indicate that cancer is getting worse.

Chemotherapy is the use of drugs to cure cancer. Chemotherapy can be administered orally or intravenously. Chemotherapy works by hindering the tumor cells' ability to grow or divide as a result the cancer cannot grow and spread. Chemotherapy is administered in a cycle for a set period of time where one or more combination of drugs is used at the same time. There are various drugs used in combination that are used to treat cancer. In the table below is the list of drugs that are used in combination [6].

Table 2 Chemotherapy Combinations

Alkylating Agents	Cyclophosphamide
	chlorambucil
	Bendamustine
	Ifosfamide
Corticosteroids	Prednisone
	Dexamethasone
Platinum Drugs	Cisplatin
	Carboplatin
	Oxaliplatin
Purine Analogs	Fludarabine
	Pentostatin
	Cladribine
Anti-metabolites	Cytarabine
	Gemcitabine
	Methotrexate
	Pralatrexate

Others	Vincristine
	Doxorubicin
	Mitoxantrone
	Etoposide
	Bleomycin

This Table shows different medicines that are used in combination with a specific function for treatment of patients. Extracted from American cancer society webpage

The most common chemotherapy used in non-Hodgkin's lymphoma is CHOP, which consists of four drugs cyclophosphamide, doxorubicin, vincristine and prednisone. Recent studies have shown that the addition of rituximab to this CHOP regimen works best for patient with B cell lymphoma [11]. Rituximab is an immunotherapy drug which is added in CHOP regimen. Other combination of drugs used in non-Hodgkin's lymphoma are FAD (Fludarabine, doxorubicin, dexamethasone) and FMD (Fludarabine, Mitoxantrone and dexamethasone). FAD and FMD are also often given with rituximab [8]. Chemotherapy comes with some side effects such as nausea, vomiting, fatigue, risk of infection, hair and appetite loss. These side effects are temporary and persist only during chemotherapy treatment and go away once chemotherapy is over.

2.11 Liver Function test

In any suspected case of the NHL blood test are carried out to see how well the liver and kidneys are working as these organs are in a lot of stress during any disease or abnormality of the body. Abnormal range of alanine aminotransferase (ALT), alkaline phosphatase (AFOS) and bilirubin in the blood can indicate some problem with the liver [21]. Diseased or damaged liver gives abnormal ALT, AFOS and bilirubin count. In this study, we have considered and included the values of ALT and AFOS measured before and after chemotherapy. These values are then correlated with the changes in SUV values before and after study for the same set of patients.

2.11.1 ALT (Alanine Aminotransferase)

Alanine Aminotransferase (ALT) is measured from blood. ALT is mainly found in liver and in small amount in other organs such as kidney, heart muscle and pancreas [22]. It is measured to see if the liver is damaged or has certain disease such as jaundice, hepatitis, cirrhosis. Diseased or damaged liver releases ALT into the blood stream which increases the ALT level in blood. Decay of large tumor also causes high ALT level. It is a reliable test to determine liver damage. However, high level of ALT does not directly equate to liver disease or injury as mentioned above it may indicate some problem with the proper functioning of the liver. Knowing the exact level of ALT does not relate to the extent of damage or disease in liver Its range is 10-70 U/L for male and 10-45 U/L for female used in this study. However, the range can vary from one test laboratory to another.

2.11.2 AFOS (Alkaline Phosphatase)

Alkaline Phosphatase (AFOS) is an enzyme found and measured from blood. This enzyme is mainly found in liver and bones. This test alone cannot indicate a problem with liver, but this test along with other liver function test can give us indication of some stress in liver due to disease or damage [23]. Its normal value ranges from 35-105 U/L for adults aged 18 or more.

2.11.3 Prothrombin time

Prothrombin time refers to ability of blood to clot in the normal way during the cut, bruising or bleeding. Clotting is an important mechanism for bleeding control and control of blood loss from the body. It is a vital component of survival for any living being. These proteins or enzymes, are mainly produced in the liver called clotting factors. Normal values of prothrombin time is 9.5 to 13.8 seconds [38].

2.11.4 Bilirubin

Bilirubin is excreted as bile from the body. Elevation of the bile level can indicate abnormal liver function. Bilirubin is a by-product when red blood cells are damaged. Despite normal liver functioning bilirubin value can also increase due to destruction of red blood cells from other condition. The normal value for bilirubin ranges from 0.1 to 1 mg/DL [38].

2.11.5 Albumin

Albumin is produced by liver alone, so abnormality in its value can indicate liver cirrhosis or liver disease. Albumin is readily found protein in blood. However, low albumin values can be caused by other conditions as well. Normal values for albumin are 3.5 to 5 g/dl [38].

3 Material and Methods

3.1 Subjects

Patients consisted of 12 male and 7 female patients, aged between 47 to 80 years, having histologically proven aggressive Non-Hodgkin's lymphoma. Patient in clinical stage II to IV, WHO performance scale better than 4 and requiring chemotherapy were included in the study. Patients with pregnancy, psychosis, diabetes, HIV infection, AIDS, primary central nervous system lymphoma or other serious medical conditions were excluded from the study. The blood glucose level is an important factor that was needed to be addressed as in patients with higher glucose level FDG uptake in delayed image is elevated [49]. PET/CT scan of the patients were taken one week before chemotherapy, one week after, one month after and three to four months after chemotherapy [16].

The images in all these cases were analyzed for changes in F-18 FDG uptake in liver before the treatment with R-CHOP and in different period after treatment. Written consent of the patients was acquired before they were included in the study; the study was also approved by the ethical committee of Tampere University Hospital. Patients then went through series of examination such as laboratory test, physical examination; computed tomography scans of the pelvis, chest and abdomen, unilateral bone marrow aspiration and trephine biopsy. After physical examination PET/CT scan of the patient was performed.

Table 3 Patient Data

Number Of Patients		Age
Male	12	48-78

Female	7	51-80
Chemotherapy	R-CHOP (19)	
Diagnosis	NHL (19)	

The table 3 illustrates the number of patients, their age, medical condition and mode of treatment in the present study.

3.2 Scanning

PET/CT scan was carried out by Discovery STE 16, GE healthcare, Milwaukee, WI, USA. Prior to scanning patient were asked to fast for 6 hours and were administered with 370 MBq of 18 F-FDG radiopharmaceutical. 18 F FDG has a half-life of 110 minutes. One hour after injecting radiopharmaceutical patients were subjected to scan from the base of the skull to the upper thigh for three minutes per bed position. The image obtained is then reconstructed with GE's 3D VUE Point reconstruction algorithm [16].

The images obtained from FDG-PET/CT was evaluated quantitatively as standard uptake value to compare tracer uptake in different part of the body. Fusion imaging was used which involves both PET images and CT images for more accurate localization. The images were viewed in HERMES workstation which allowed multiple tools for viewing, manual and automatic segmentation.

3.3 ROI selection and SUV measurement

The activity in the liver had to be quantified using standard uptake value (SUV). In such a scenario, there were a few techniques that could be applied to get the true maximum standard uptake value (SUVmax) and mean standard uptake value (SUVmean) values for liver. One of the technique was to select the whole liver volume in 3D and measure the desired value. The method used in this research was to select transverse slices along the length of the liver after certain interval which covered the entire volume of the liver. Fusion imaging mode was used where we could view and analyze computed tomography and positron emission tomography images dependently and independently.

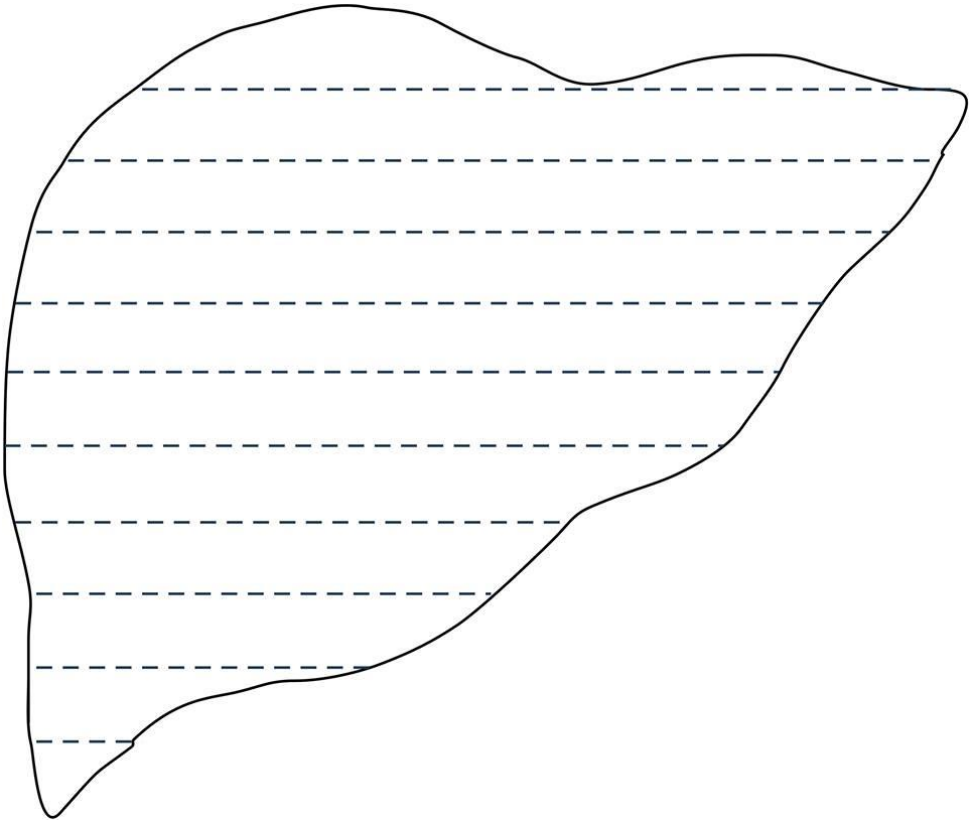

Figure 3-1 Liver Transverse slice

Transverse slices in liver were selected in uniform interval along the volume of the liver to get more consistent results for all the image studies, as shown in figure 3-1.

The selection of liver ROI using only PET was tricky and subject to error. So, computed tomography was used to select transverse slices at every 10 mm thickness. Region of interest was then manually selected in each of the transverse slices. To make the measurement more reliable region of interest was made constant wherever possible for consecutive slices provided the region was well inside the liver boundary. Manual segmentation of the slices was challenging, but the use of computed tomography to locate the exact boundary of the liver simplified the task, moreover it made the obtained standard uptake value of the liver more reliable.

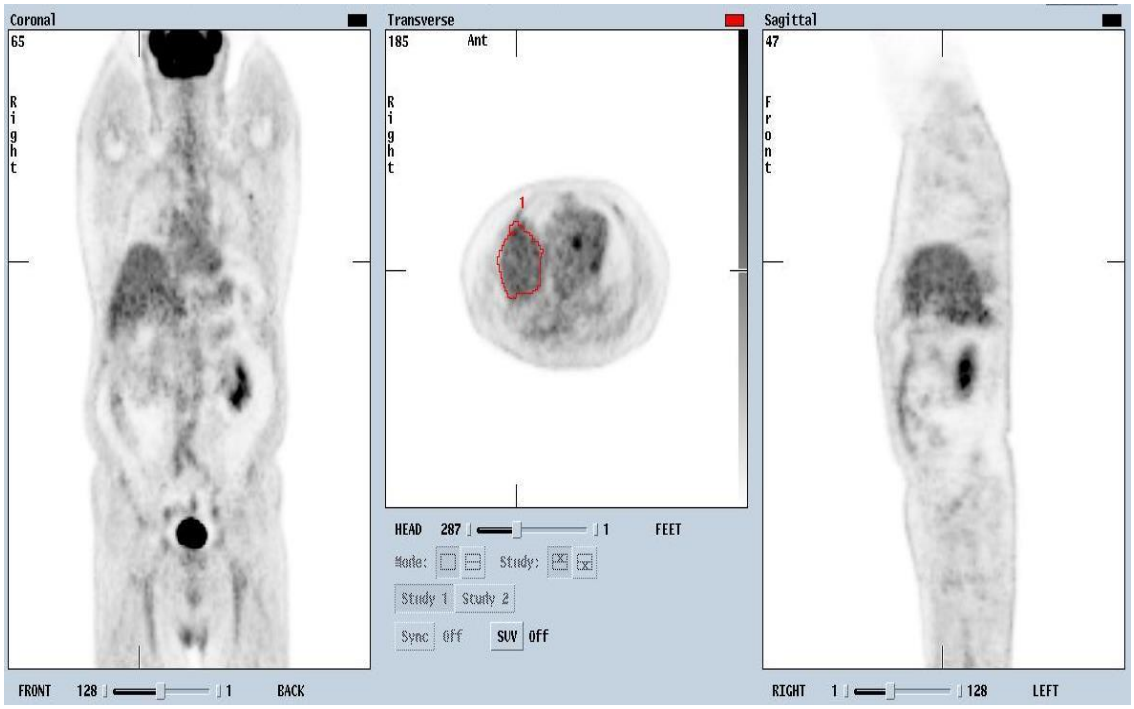

Figure 3-2 Manual Segmentation

Manual selection of transverse liver slice as shown in figure 3-2 to obtain mean and max standard uptake value along with coronal and sagittal view of the patient to better facilitate ROI selection in HERMES workstation.

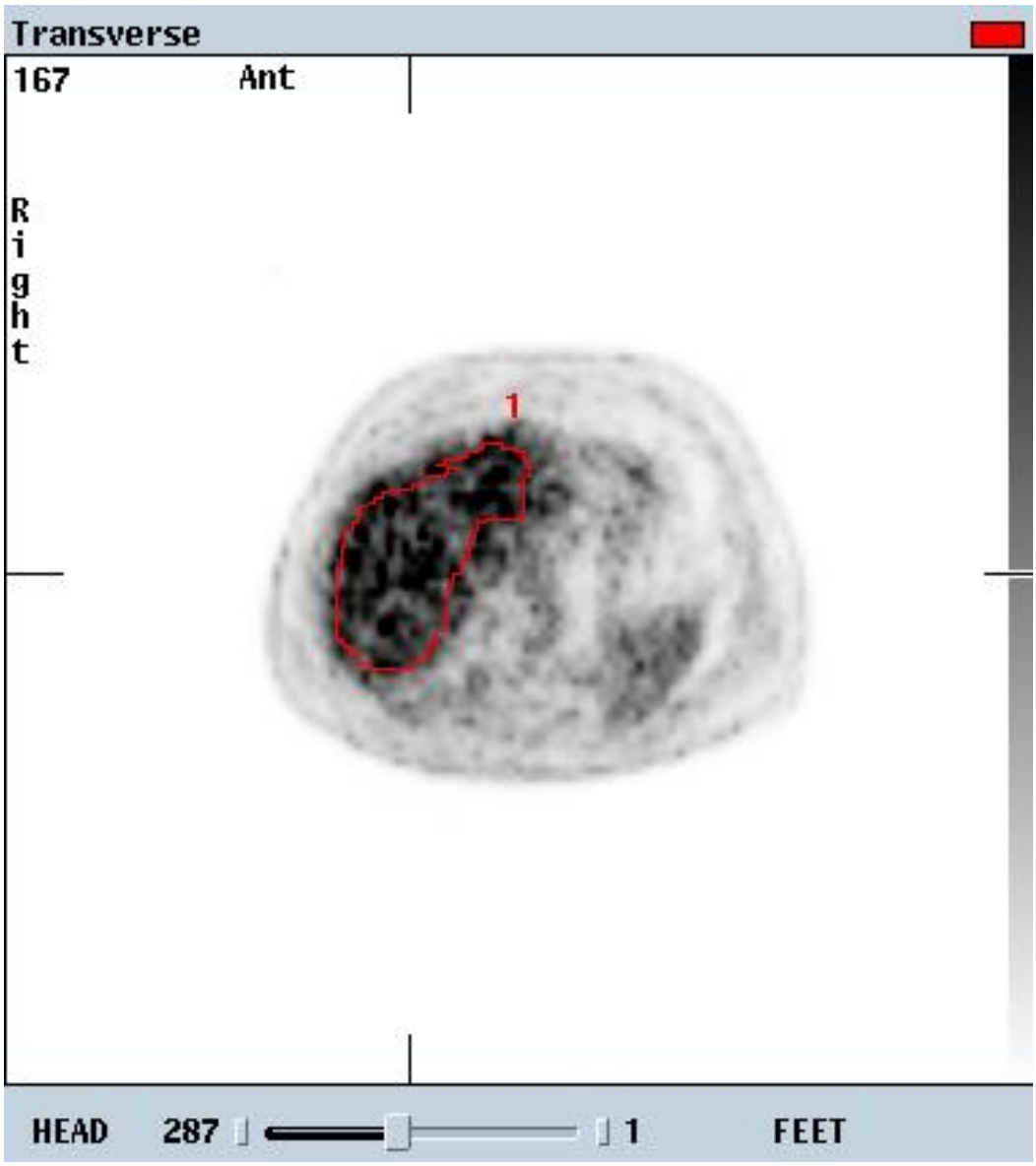

Figure 3-3 ROI selection

Figure 3-3 shows manual transverse liver slice selection to obtain SUV values in an FDG-PET scan on HERMES workstation. The standard uptake value of the selected region of interest was obtained.

To be exactly precise fusion imaging technique was applied, which used computed tomography and positron emission tomography so that only the liver slices were selected and other structures were not included in the ROI.

3.4 Statistical Analysis

Statistical analysis is a vital component of the whole analysis. The standard uptake value of the liver slices obtained from the Hermes workstation had to be processed to obtain the standard uptake value of the whole liver not the slices. The region of interest in liver slices was selected and assessed using standard protocol. To obtain the SUV of whole liver volume, mean of the all the slices was calculated which is represented as SUVmean in our study. The maximum SUV however, was selected among the highest registered SUV among all slices.

The study included 19 patients each with four PET/CT scans one before administrating chemotherapy and three scans after chemotherapy. 76 scans were studied in the process to obtain the mean and maximum standard uptake value of liver in each case. IBM SPSS 22 software was used to statistically analyze the changes in mean and maximum SUV before chemotherapy and after chemotherapy. Liver function tests were also carried out for patients during the time of the scan. In this study, we have included ALT and AFOS value at baseline and one month after chemotherapy, which was taken from the patients' blood sample on the same day of the scan. The paired T test was used to assess if the changes in the enzymes value varied significantly before and after chemotherapy. The paired T test was also used to see changes in the SUV mean and SUVmaximum value during the same time period.

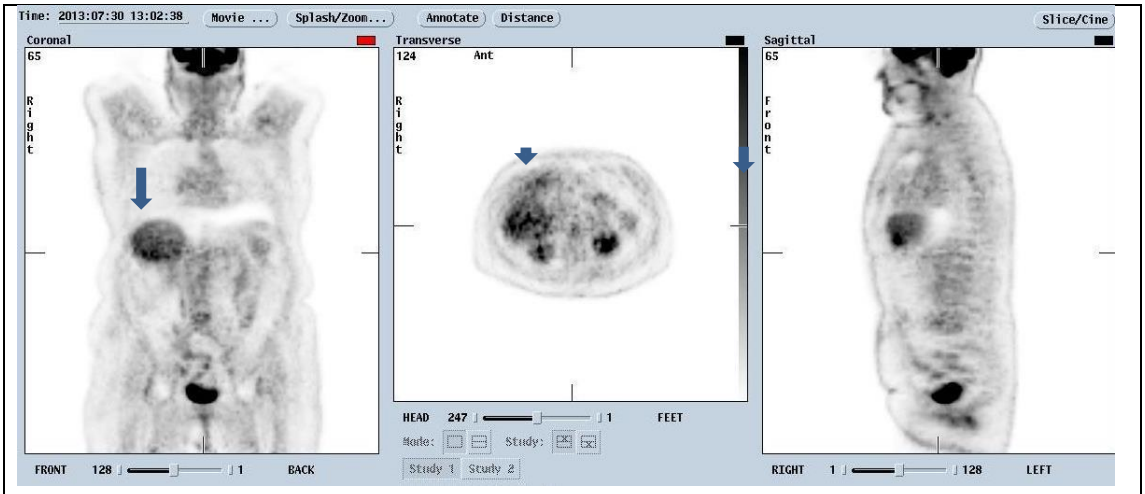

Figure 3-4: Baseline (E1)

PET/CT scans showing coronal, transverse and sagittal slice of patient before chemotherapy as illustrated in figure 3-4. Arrow indicating liver, which is the region of interest in our study.

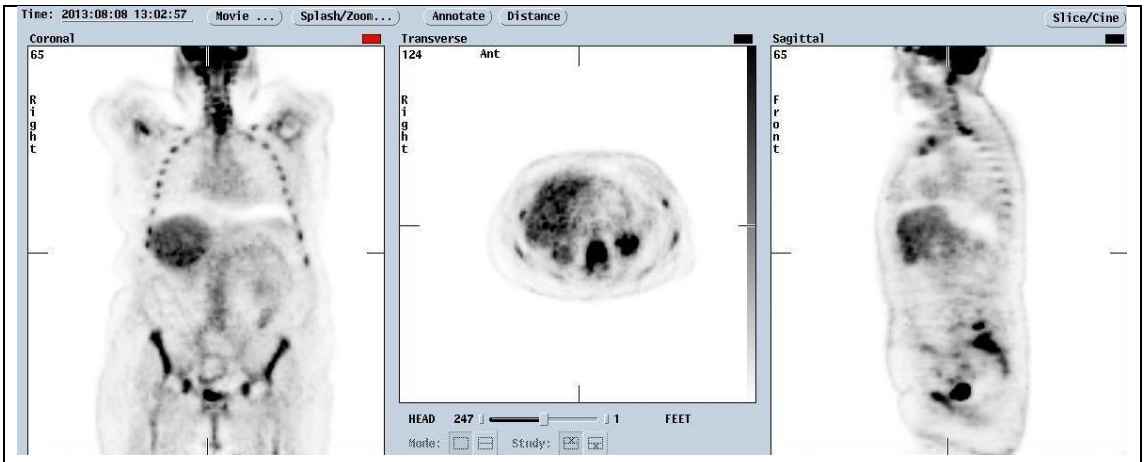

Figure 3-3-5 : One week after Chemotherapy (E2)

PET/CT scans showing coronal, transverse and sagittal slice of patient one week after chemotherapy, as illustrated in figure 3-5.

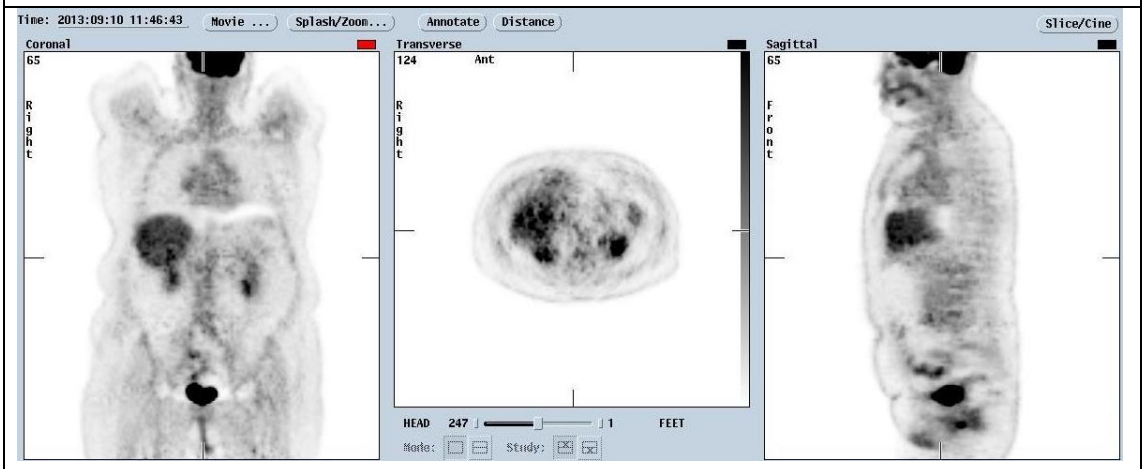

Figure 3-6: One month after chemotherapy (E3)

PET/CT scans showing coronal, transverse and sagittal slice of patient one month after chemotherapy, as shown in figure 3-6.

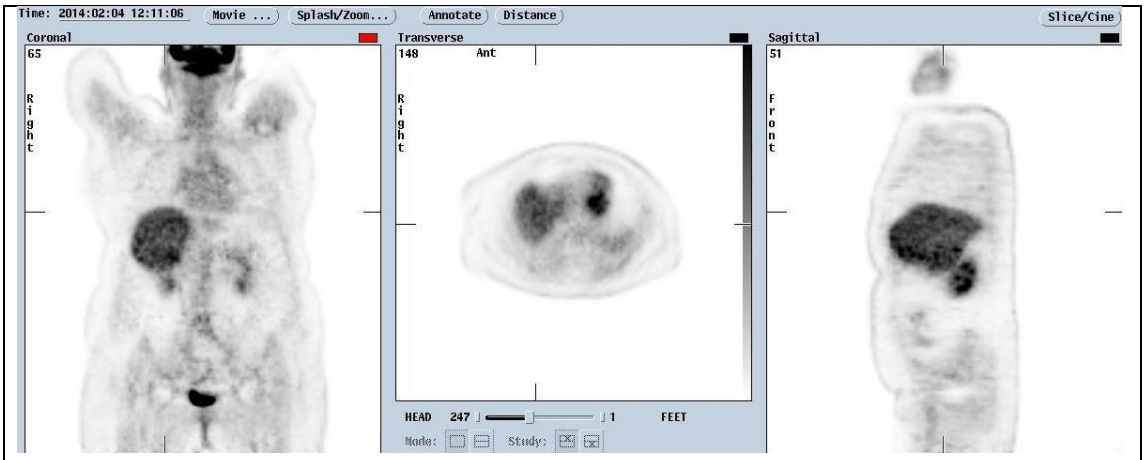

Figure 3-7:Four months After chemotherapy (E4)

Figure 3-7 PET/CT scans showing coronal, transverse and sagittal slice of patient four months after chemotherapy.

The difference in result is determined using p value. P value less than 0.05 represents there is a significant difference between the mean of the tested values. If the p value is more than 0.05 it represents there is no significant difference in the mean values before and after treatment.

4 Results

4.1 Mean and Maximum SUV of Liver

The table below shows the mean and maximum liver standard uptake value obtained after manual segmentation of transverse liver slices from PET/CT scan of all 19 patients. In the study, PET/CT scan was taken before chemotherapy and three scans were carried out after chemotherapy. As we can see from the table some of the patients did not appear for certain PET/CT scans after chemotherapy, but we still decided to include them in the study as it may not affect the outcome of the study considerably.

Table 4 Mean and Maximum SUV of Liver

	Mean SUV				Maximum SUV			
Patient	E1	E2	E3	E4	E1	E2	E3	E4
1	1,6745	1,7323	2,0177	1,8864	1,0814	4,2412	3,0270	3,2980
2	1,9366	1,8596	1,9623	2,1268	1,2969	4,4780	3,2200	3,1050
3	1,9752	-	1,9021	1,8608	1,3100	-	3,0180	4,7610
4	1,8088	1,9826	1,5061	2,2395	1,0604	3,2200	2,8680	4,0950
5	1,4604	1,7713	1,6295	1,9649	,6651	3,5350	2,5180	2,9540
6	1,9942	-	2,2577	1,9498	,8800	-	3,8970	3,8020
7	2,3139	2,3257	2,4822	2,4744	1,2317	3,2900	4,1820	3,6030
8	2,1142	1,9956	2,2564	2,7626	1,4317	3,0420	4,1190	4,1810
9	1,3328	1,7352	1,6175	1,8353	,5126	2,5580	2,7460	2,8040
10	1,5219	1,9509	1,8043	2,0160	,8506	3,1520	3,5810	3,3920
11	1,7063	1,4437	1,8447	1,7990	1,1899	2,1110	2,5390	2,8510
12	1,2971	1,8998	-	1,7204	,6500	2,9710	-	3,7460
13	2,0317	2,4440	2,2881	1,9453	,9478	3,3310	3,6230	2,8950
14	2,3614	2,4403	2,4453	2,3676	1,0870	3,6370	3,8950	4,0180

15	2,0700	2,0367	2,2817	2,3599	1,2184	3,3320	3,9780	3,5790
16	1,9690	1,9029	2,2173	2,2751	,9304	3,8290	4,2950	3,8520
17	2,6505	2,5156	2,5562	2,3357	1,6702	5,0160	4,7240	4,3590
18	3,0756	2,9858	2,9632	3,2795	,8000	6,1510	5,8350	5,1410
19	1,8342	1,8214	2,0340	2,0691	1,1052	2,8215	3,0777	3,1972

Table shows mean and maximum standard uptake value for liver for 19 patients at baseline (E1), one week after chemotherapy (E2), one month after chemotherapy (E3) and four months after chemotherapy (E4).

4.2 Liver SUV Mean before and after treatment

Mean liver standard uptake value is compared using a paired T test before treatment and after different cycles of administering R-CHOP chemotherapy. The test is carried out using IBM SPSS 22 software. Comparing means before treatment and one week after chemotherapy we obtained a P value of 0.109. Significance limit in our hypothesis has $\alpha = 0.05$, which is smaller than our obtained P value. Hence, we can say that there is no significant difference in the mean SUV before treatment and one week after treatment.

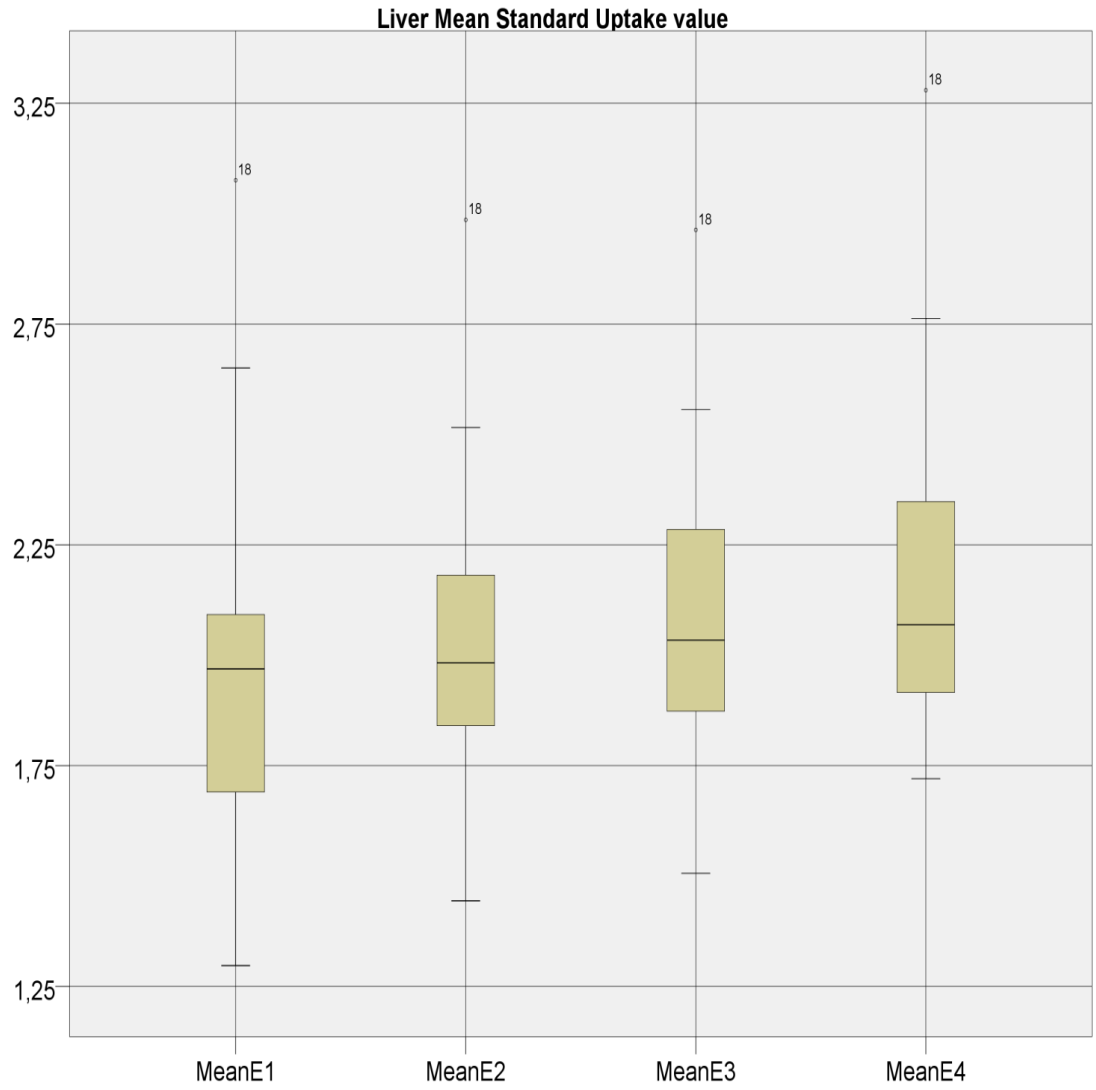

Figure 4-1: Mean SUV

Plot 4-1 shows mean standard uptake value for liver at baseline (E1), one week after chemotherapy (E2), one month after chemotherapy (E3) and four months after chemotherapy. The black line in each box indicates the mean of liver SUV means.

A similar test is carried out and SUV before treatment is compared to one month and four months after treatment. The mean standard uptake value one month and four months after treatment was highly significant, where calculated P value was 0.005 and 0.001 respectively when compared to baseline PET/CT. We could infer that there is a noticeable change in the mean standard uptake value in that period.

Table 5: T paired Test mean SUV

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	MeanE1 - MeanE2	-,09027	,23363	,05360	-,20287	,02234	-1,684	18	,109
Pair 2	MeanE1 - MeanE3	-,15463	,21375	,04904	-,25766	-,05161	-3,153	18	,005
Pair 3	MeanE1 - MeanE4	-,21788	,25231	,05788	-,33949	-,09628	-3,764	18	,001
Pair 4	MeanE2 - MeanE3	-,06436	,21930	,05031	-,17006	,04134	-1,279	18	,217
Pair 5	MeanE2 - MeanE4	-,12762	,27600	,06332	-,26064	,00541	-2,015	18	,059
Pair 6	MeanE3 - MeanE4	-,06325	,28155	,06459	-,19896	,07245	-,979	18	,340

Paired sample T test carried out on mean standard uptake value obtained at baseline (E1), one week after chemotherapy (E2), one month after chemotherapy (E3) and four months after chemotherapy (E4) in the liver. Sig represents a significance level calculated from the test carried out on IBM SPSS 22.

After chemotherapy started on the patient, we again evaluated the changes in liver SUV. Three distinct PET/CT studies were carried out one week, one month and four months after treatment. Mean SUV of all the studies was compared and we could statistically see that there was no significant change in the mean SUV value. The complete table for t pair test is attached in appendix. This study demonstrates that after administrating R-CHOP chemotherapy the mean liver standard uptake value did not change when compared to one month and four months after chemotherapy.

4.3 Liver SUV max before and after treatment

A paired T test was carried out in IBM SPSS 22 software to statistically test the changes in maximum standard uptake value before treatment and after chemotherapy in liver. All cases were tested in pairs to find if there was any significant difference in the liver maximum SUV value. Correlation between liver function test and standard uptake value of liver was carried out using MedCalc software.

Table 6: Paired T test Maximum SUV

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	MaxE1 - MaxE2	,62136	3,07252	,70488	-,85954	2,10227	,882	18	,390
Pair 2	MaxE1 - MaxE3	,49363	2,95038	,67686	-,92841	1,91566	,729	18	,475
Pair 3	MaxE1 - MaxE4	,36255	3,03370	,69598	-1,09965	1,82475	,521	18	,609
Pair 4	MaxE2 - MaxE3	-,12774	,84584	,19405	-,53542	,27994	-,658	18	,519
Pair 5	MaxE2 - MaxE4	-,25882	1,00352	,23022	-,74250	,22486	-1,124	18	,276
Pair 6	MaxE3 - MaxE4	-,13108	,72865	,16716	-,48228	,22012	-,784	18	,443

Paired sample T test carried out on the maximum standard uptake value obtained at baseline (E1), one week after chemotherapy (E2), one month after chemotherapy (E3) and four months after chemotherapy (E4) in the liver. Sig represents a significance level calculated from the test carried out on IBM SPSS 22.

There was no significant difference in the maximum standard uptake value in all the cases. The test result attached in appendix clearly shows no significant rise in the maximum SUV value in all the cases before and after treatment.

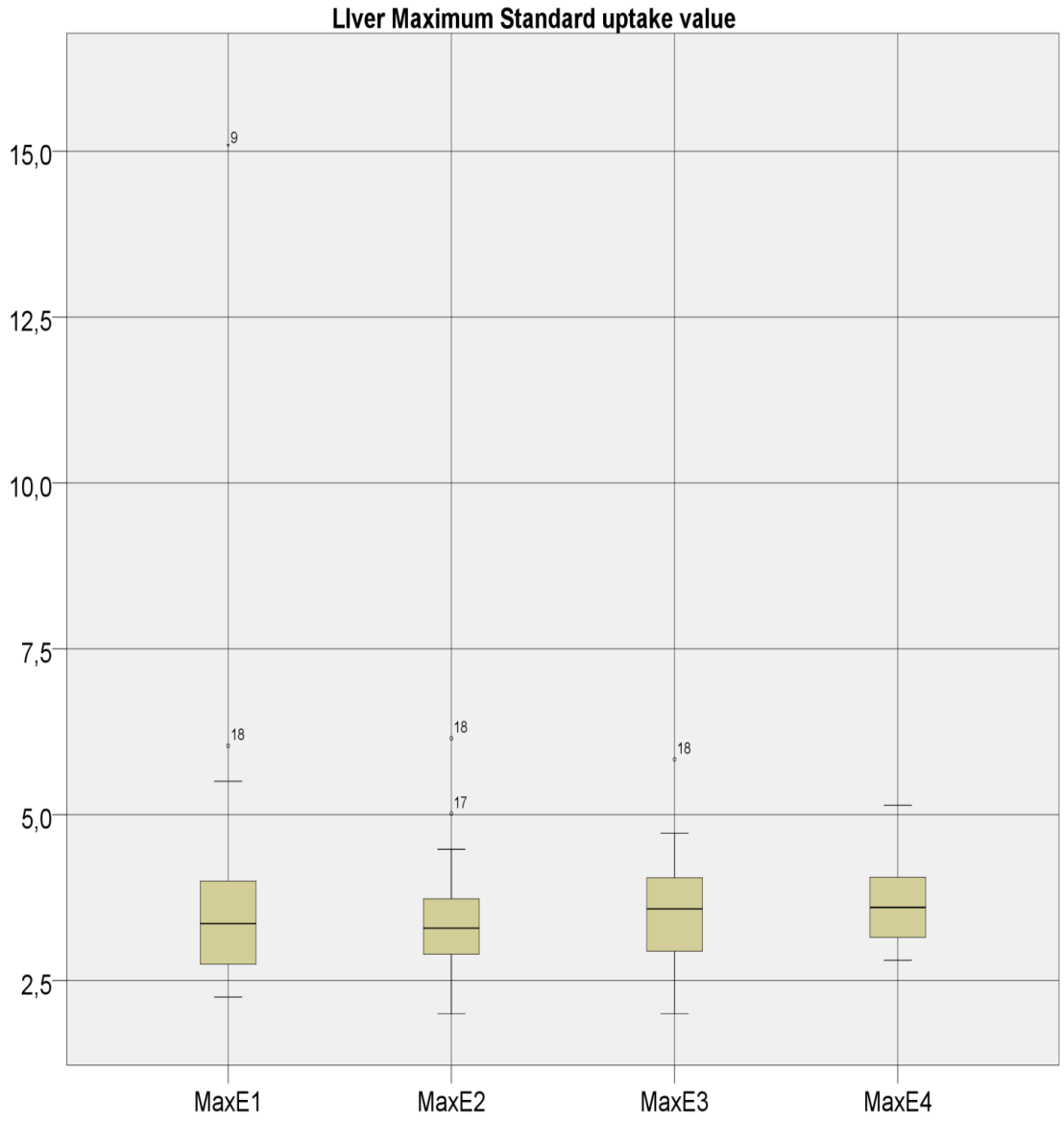

Figure 4-2: Maximum SUV

Plot 4-2 shows maximum standard uptake value for liver at baseline (E1) one week after chemotherapy (E2) one month after chemotherapy (E3) and four months after chemotherapy in liver. The black line in each box indicates the mean of liver SUV maximum.

4.4 Liver Standard Uptake Value and Liver Function Test

4.4.1 Mean SUV and Alanine Aminotransferase:

Liver function test helps to determine and show us any abnormality that may persist in the liver due to disease or injury. It is very common for liver to show stress during such period which is reflected in the abnormal or high level of some enzyme in blood. In this study alanine aminotransferase (ALT) and alkaline phosphatase (AFOS) are the two enzymes included which are vital components of liver function test. ALT is mainly found in liver and in small amounts in other organs. AFOS are also found mainly in liver and bones. So, examining the level of these enzymes can give us vital clues as in relation to the condition of the liver. ALT and AFOS enzyme level in blood is examined before and after chemotherapy, in order to see if any pattern or relation between these values that may help in future diagnosis of diffuse large B cell lymphoma. In the plot below, we have taken mean standard uptake value of liver before treatment and one month after treatment. At the same time each patient went through

liver function tests on the same day of the scan. The result is shown in the plot below.

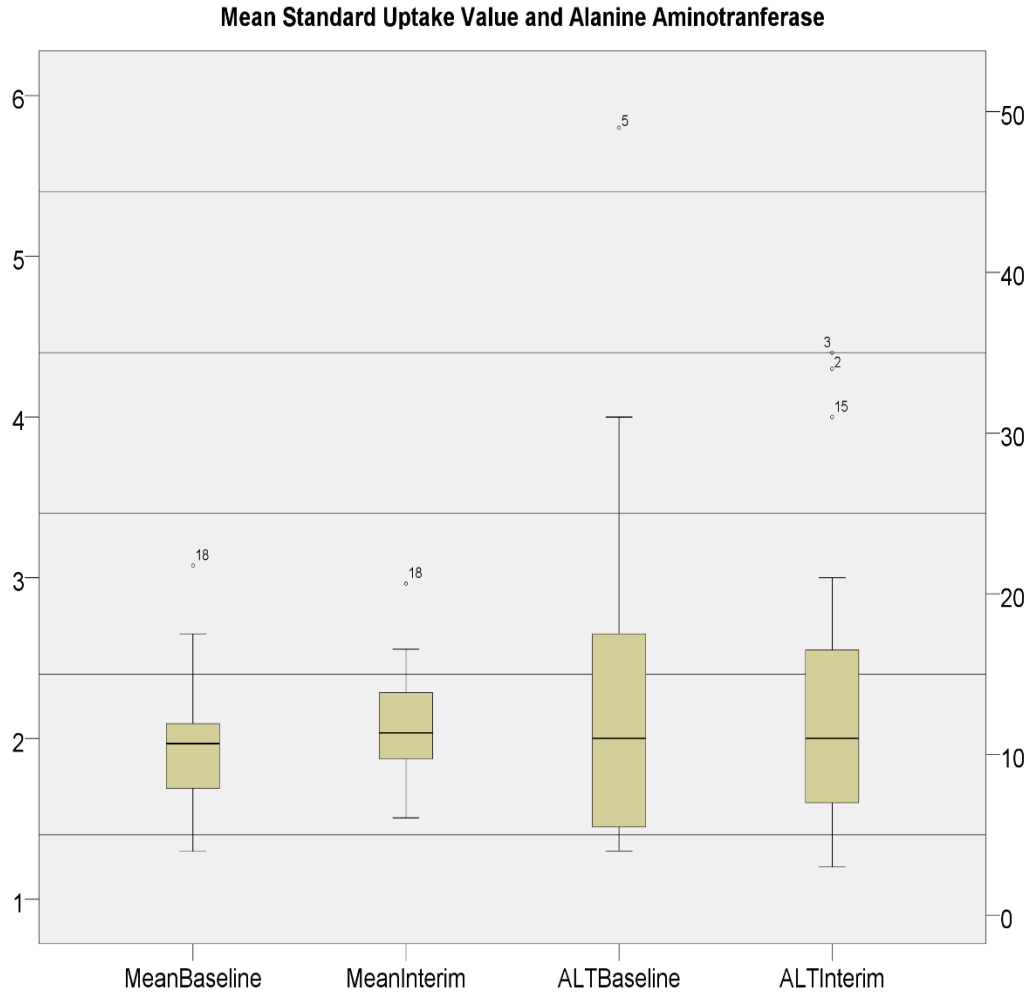

Figure 4-3: Mean SUV and ALT

Plot 4-3 shows changes in mean standard uptake value at baseline and one month after chemotherapy on the left and also changes in alanine aminotransferase value at baseline and one month after chemotherapy on the right.

When liver mean SUV is compared between the baseline period and interim period, it increased from 1.95 to 2.10, this value has been discussed more elaborately in the previous section, whereas in the same period the mean value of alanine aminotransferase has decreased slightly from to 23.63 to 23.10. A T paired test was carried out to see if the change is significant and up to a considerable level.

Table 7: Paired T Test ALT before and after chemotherapy

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1 ALT-E1 - ALT-E3	,52632	14,27651	3,27526	-6,35474	7,40737	,161	18	,874

We assumed significant value to be below 0.05 i.e. ($\alpha<0.05$). P value of 0.874 was obtained in ALT T paired test which indicates and statistically shows that the there is no significant change in alanine aminotransferase value before chemotherapy and after chemotherapy.

Correlation between mean SUV at baseline and alanine aminotreansferase was calculated using medcalc software and correlation coefficient was -0.4875 with significance level 0.0401 at baseline.

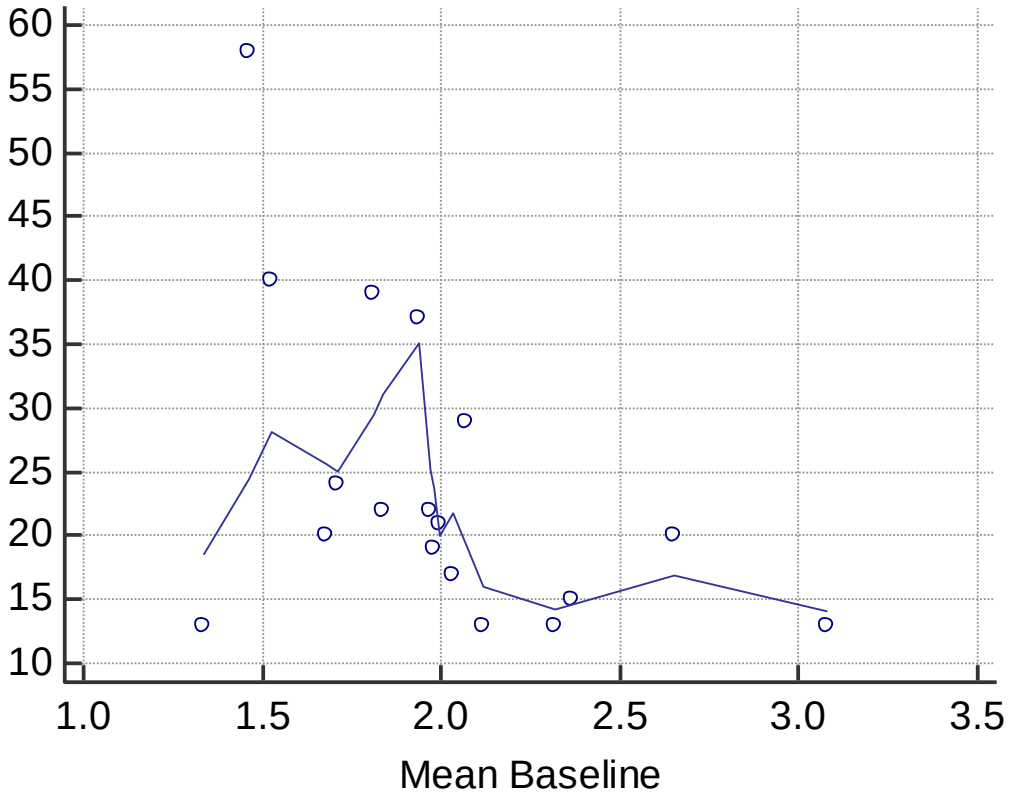

Figure 4-4: ALT and Mean SUV correlation at baseline

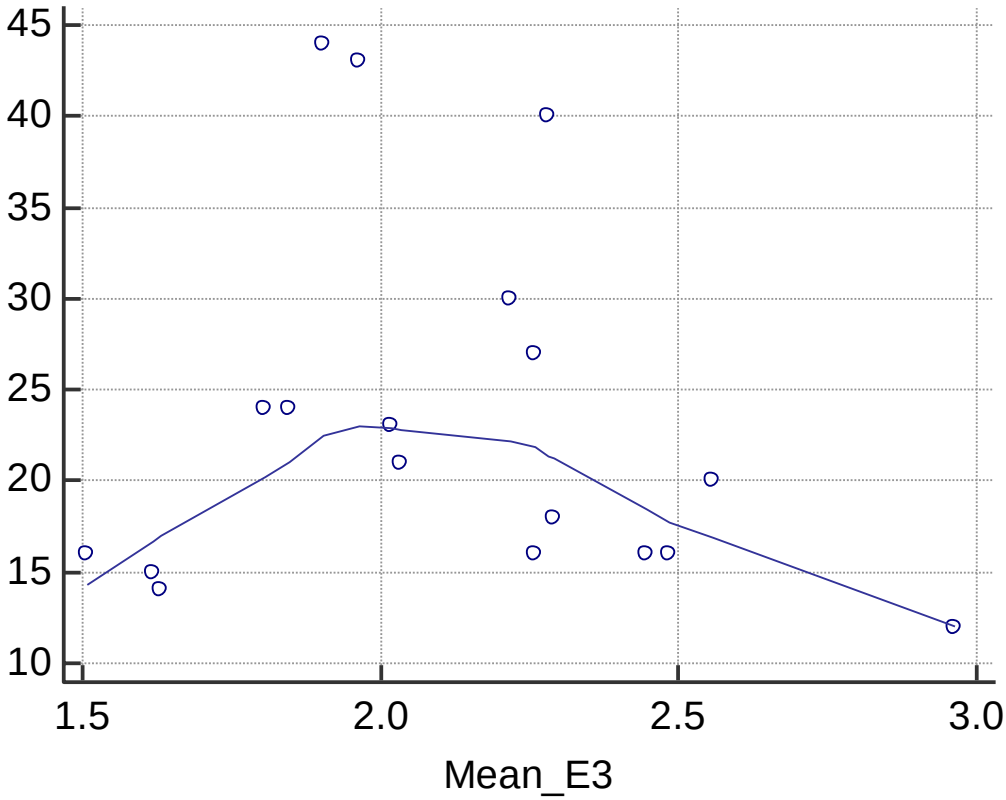

Figure 4-5: ALT and Mean SUV one month after chemotherapy correlation

Similarly correlation coefficient one month after administrating chemotherapy was -0.1356 with significance level of 0.5917. As we can see there is negative correlation in both the study before and after chemotherapy. Howevr, the correlation in both the cases is insignificant.

4.4.2 Maximum SUV and Alanine Aminotransferase

The relation between liver maximum SUV and alanine aminotransferase was also analyzed to see the possibility of some interesting relation or pattern. Analyzing the mean of maximum liver SUV, the interim mean of liver maximum SUV seen was 3.533 which decreased when compared to baseline values of 4.0275. When paired T test was used using the same hypothesis as mentioned above to see the significance level in the obtained values between baseline and interim period, the P value obtained was 0.475. This shows no significant change in the liver maximum SUV. As we calculated above the significance value for ALT before and after treatment is 0.874. Even though both the mean of liver maximum SUV and mean alanine aminotransferase values decreased from baseline to the interim period, those values did not change significantly.

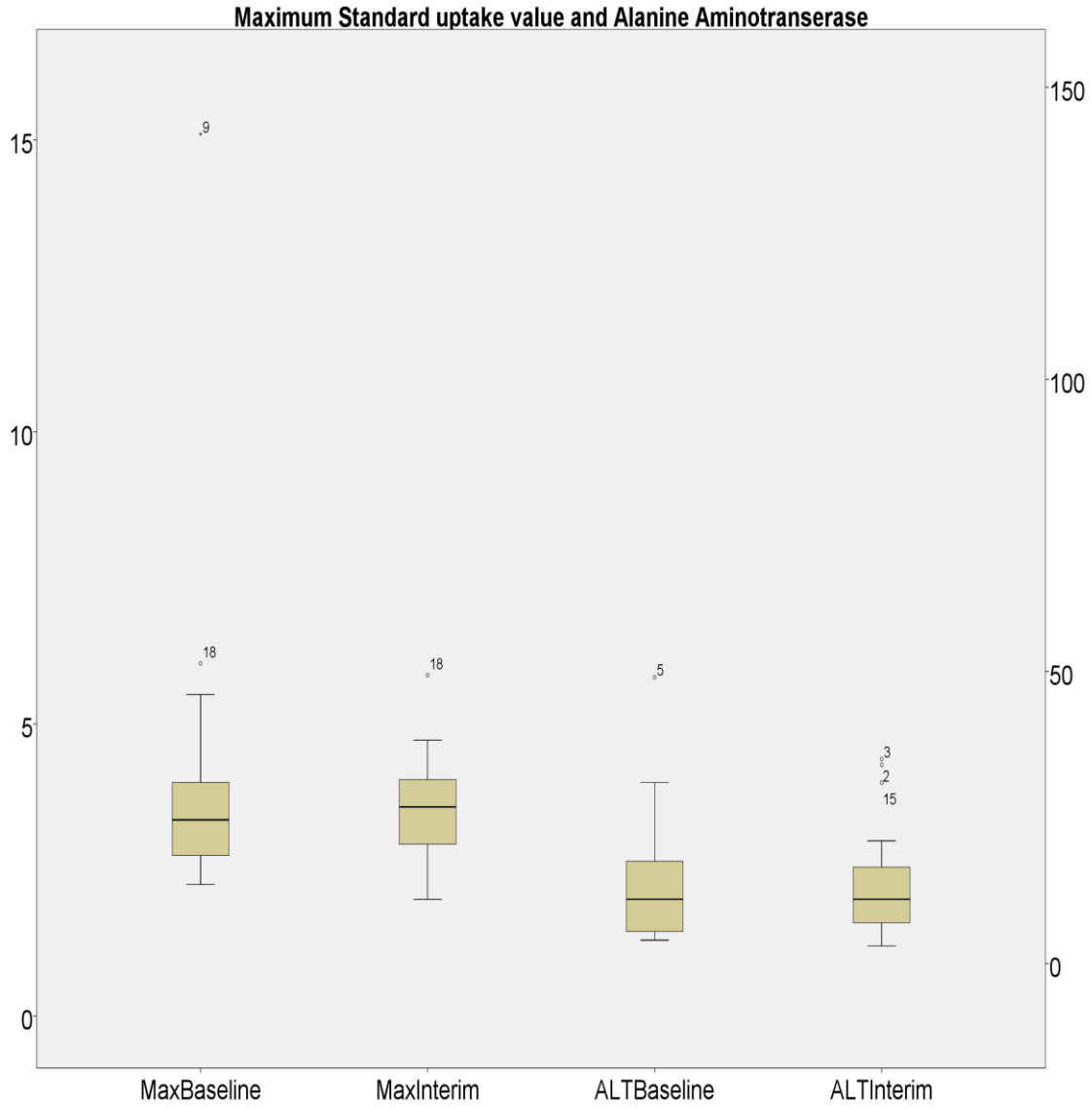

Figure 4-6: : Maximum SUV and ALT

Plot 4-6 showing changes in maximum standard uptake value at baseline and one month after chemotherapy on the left of the plot and also changes in alanine aminotransferase value at baseline and one month after chemotherapy on the right.

Correalation between maximum suv and alanine aminotransferase was calculated using MedCalc statistical software, and the obtained correalation coefficient was -0.3785 with significance level of 0.1214.

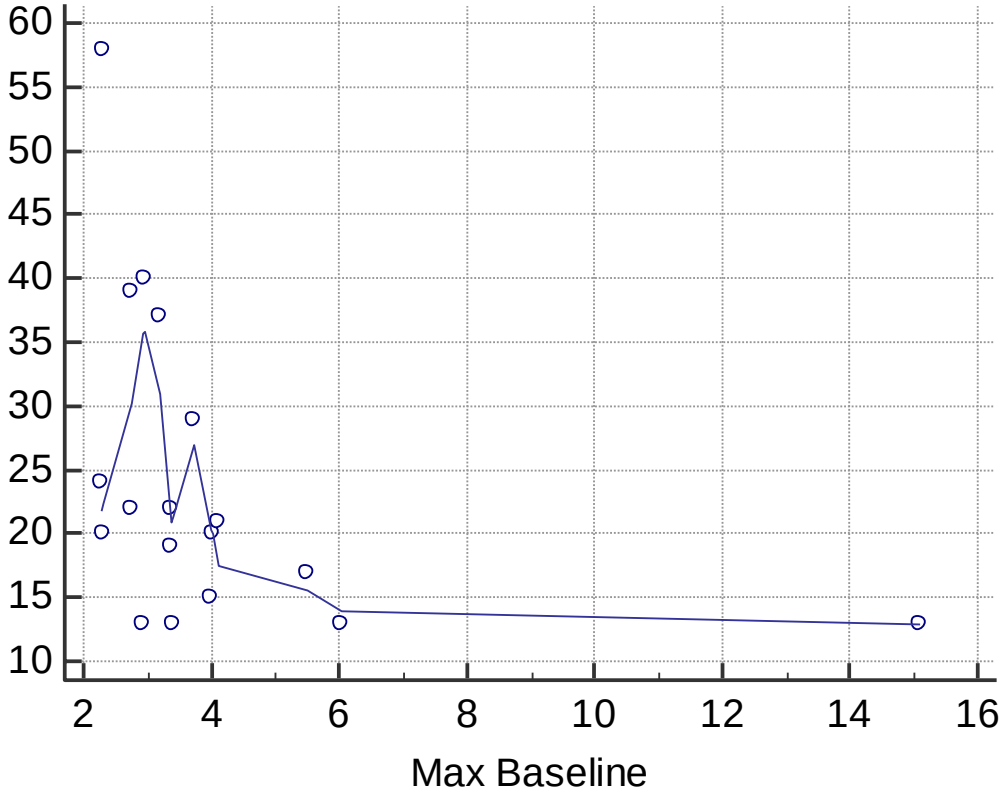

Figure 4-7: ALT AND SUV max at baseline

Similarly correlation coefficient one month after chemotherapy between maximum liver SUV and alanine aminotransferase was -0.1635 with significance level of 0.5167.

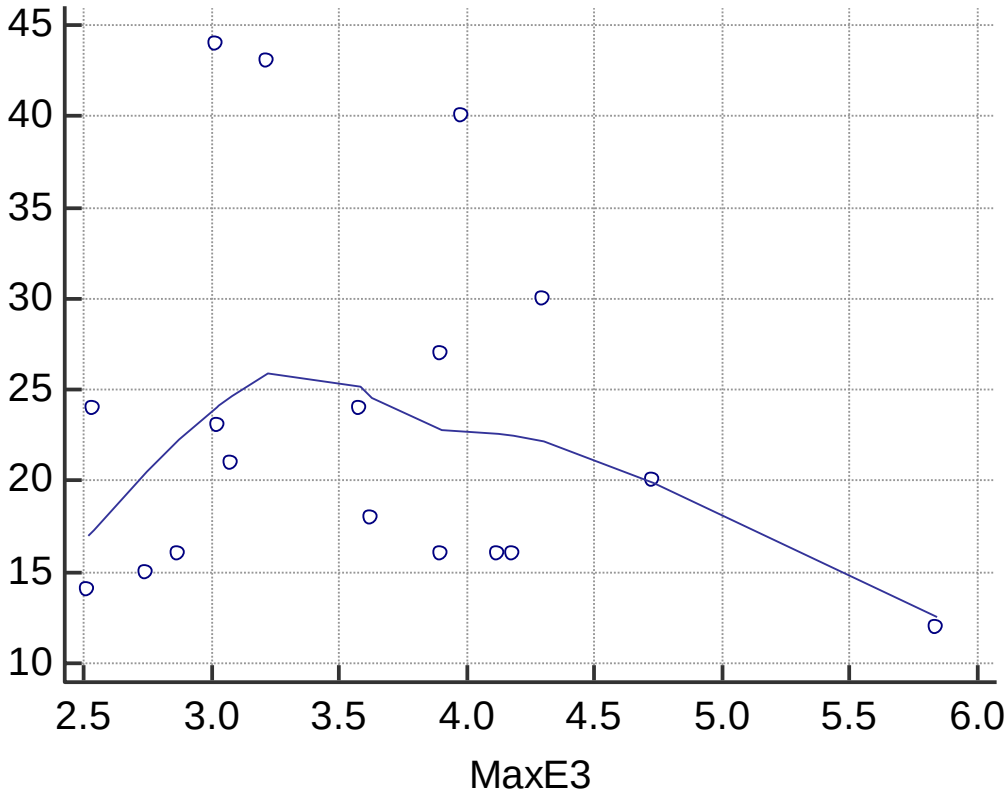

Figure 4-8: ALT and SUV max correlation one month after chemotherapy.

4.4.3 Mean SUV and Alkaline Phosphatase

Another liver function test that was included in the study was alkaline phosphatase. Alkaline phosphatase (AFOS) is mainly found in liver and bones. The abnormal AFOS level indicates some problem related to bones or normal functioning of the liver. So, abnormal AFOS level can give us some indication regarding diseased, damaged liver under some stress. AFOS values were obtained from a blood sample from the patient before the chemotherapy i.e. baseline and one month after chemotherapy when the PET/CT scan was taken. As with ALT values we compare it with mean SUV of the liver.

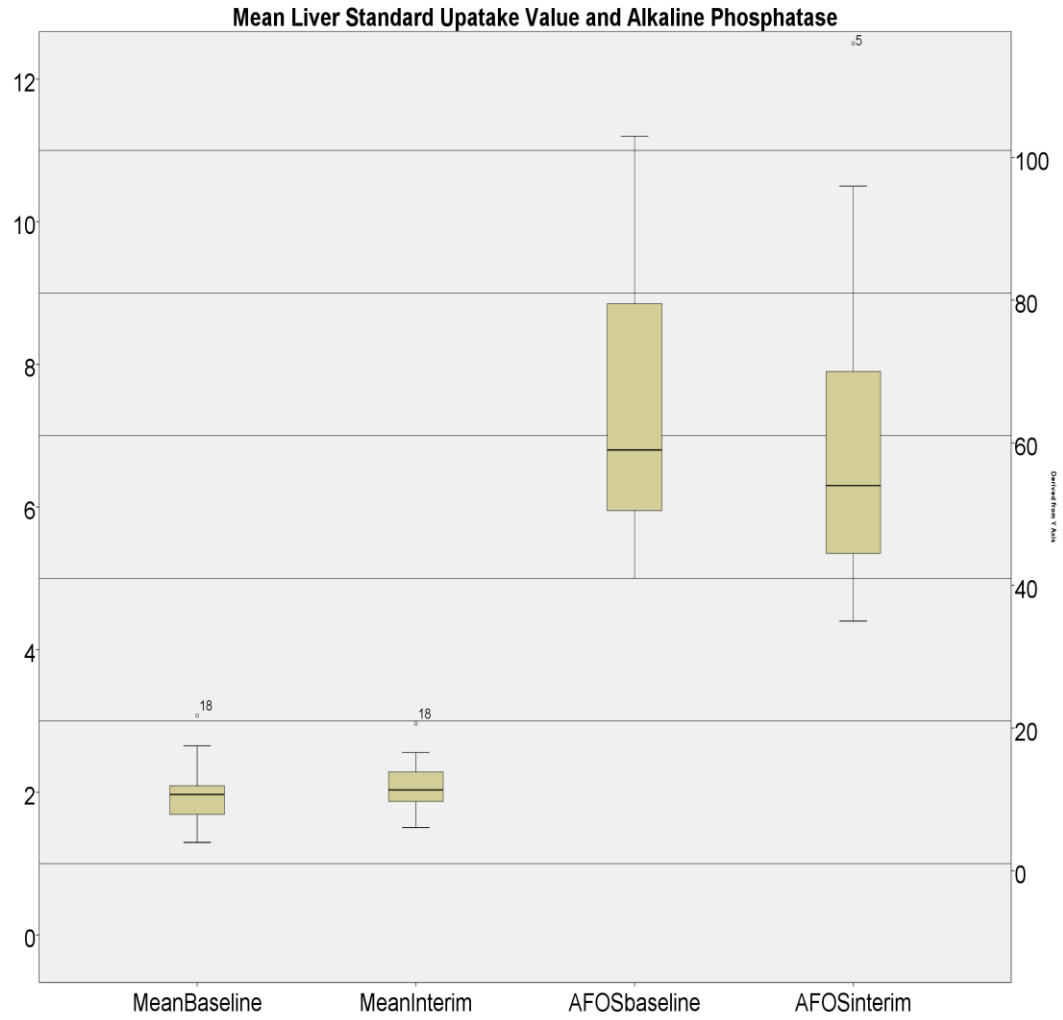

Figure 4-9: Mean SUV and AFOS

Plot 4-9 showing changes in mean standard uptake value at baseline and one month after chemotherapy on the left and also changes in alkaline phosphatase value at baseline and one month after chemotherapy on the right.

As we have discussed above the mean liver SUV has increased from baseline to interim PET level in the same period mean AFOS level has decreased from 80.474 at baseline level to 70 at interim level. The paired T test was used to see if the change in AFOS value was significant.

Table 8: Paired T test AFOS before and after chemotherapy

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	AFOS-E1 - AFOS-E3	10,47368	26,44358	6,06657	-2,27172	23,21908	1,726	18	,101

P value of 0.101 was obtained which is greater than our assumed alpha value of 0.05. So, no significant change in AFOS value can be seen from the baseline period to interim periods after chemotherapy.

Correation coefficient between mean liver suv and alkaline phosphatase was calculated before and after chemotherapy using MedCalc statistical software.

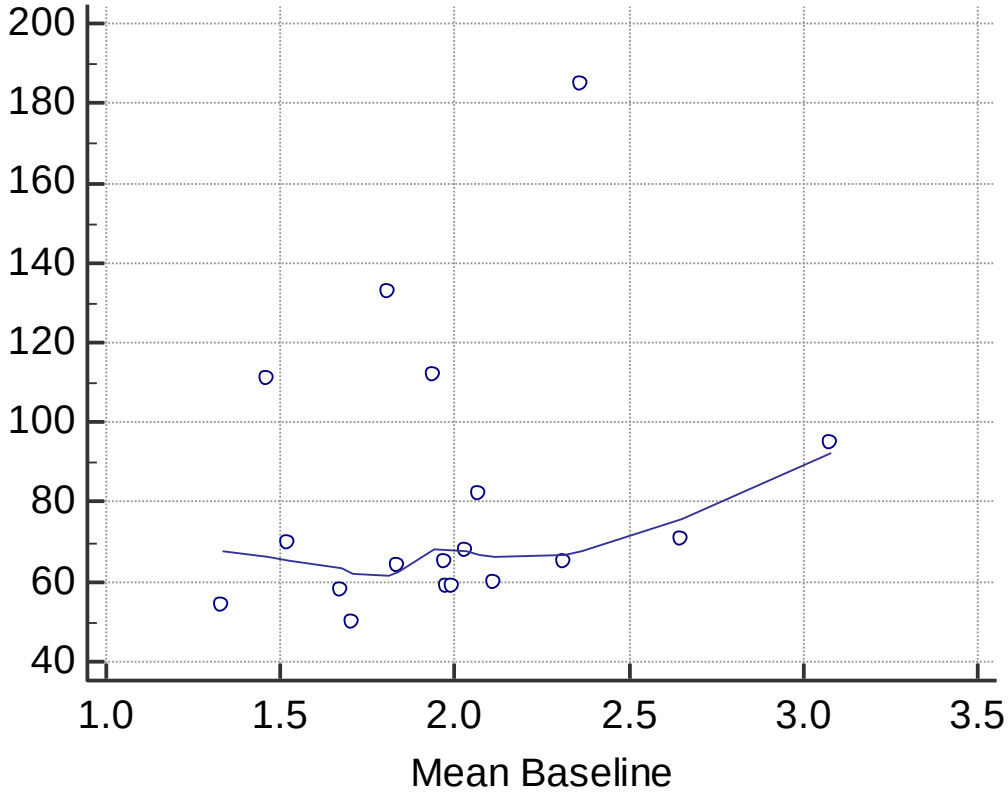

Figure 4-10: AFOS and mean SUV at baseline correlation

Correlation coefficient changed from 0.2170 to -0.2069 before and one month after chemotherapy respectively. The shift from positive to negative correlation after chemotherapy is noticeable. However, the change was not significant with significance level of 0.3870 at baseline and 0.4257 one month after chemotherapy.

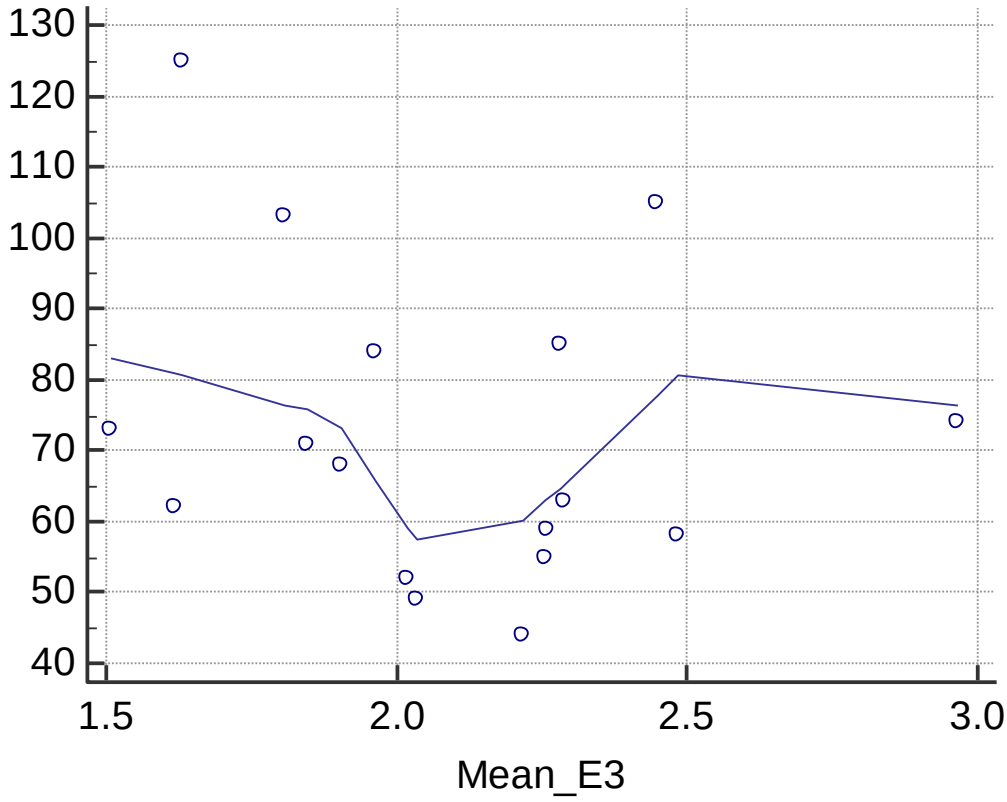

Figure 4-11: AFOS and mean SUV one month after chemotherapy correlation

4.4.4 Maximum SUV and Alkaline Phosphatase

Maximum liver standard uptake value and alkaline phosphatase level was also compared and analyzed to see if we could see some noticeable difference or change. The maximum liver SUV decreased from baseline to interim from 4.0275 to 3.5338 respectively. When paired T test was used to see the significance level in the obtained values between baseline and interim period, the P value obtained was 0.475, which shows no significant change. Similarly, as we did paired t test for AFOS as mentioned above and obtained a value of 0.101. It can be seen that even though both the maximum liver SUV value and AFOS value decreased from baseline to interim period the change in their values was not so significant. Hence, we get an indication that even though the value changed from baseline to interim period the change in values seen is insignificant.

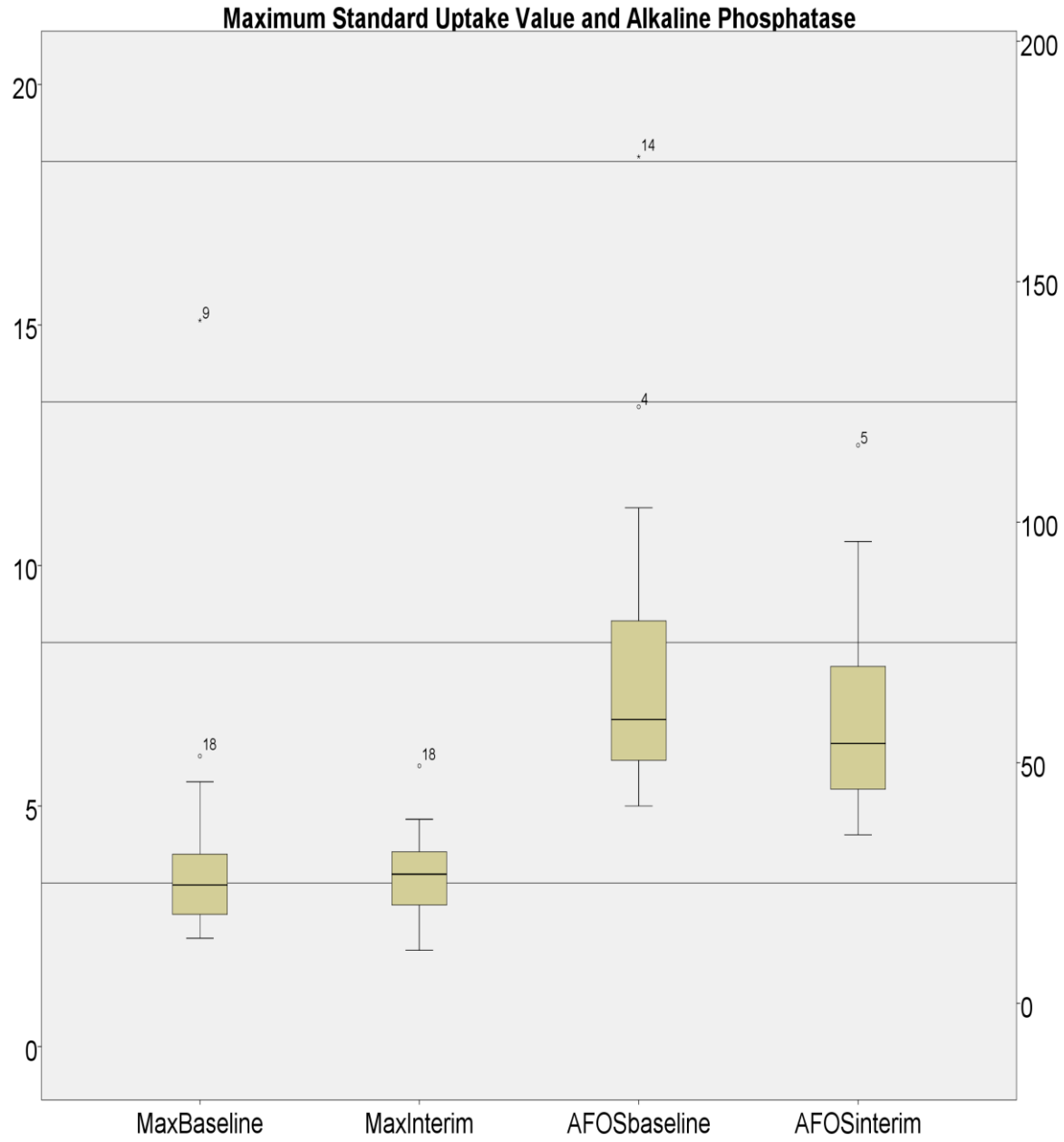

Figure 4-12: Maximum SUV and AFOS

Plot 4-12 showing changes in maximum standard uptake value at baseline and one month after chemotherapy on the left and also changes in alkaline phosphatase value at baseline and one month after chemotherapy on the right.

The correlation between maximum SUV and alkaline phosphatase was performed and we obtained correlation coefficient of -0.1469 and -0.1676 at baseline and one month after chemotherapy using MedCalc statistical software. However, correlation in both the instances were insignificant.

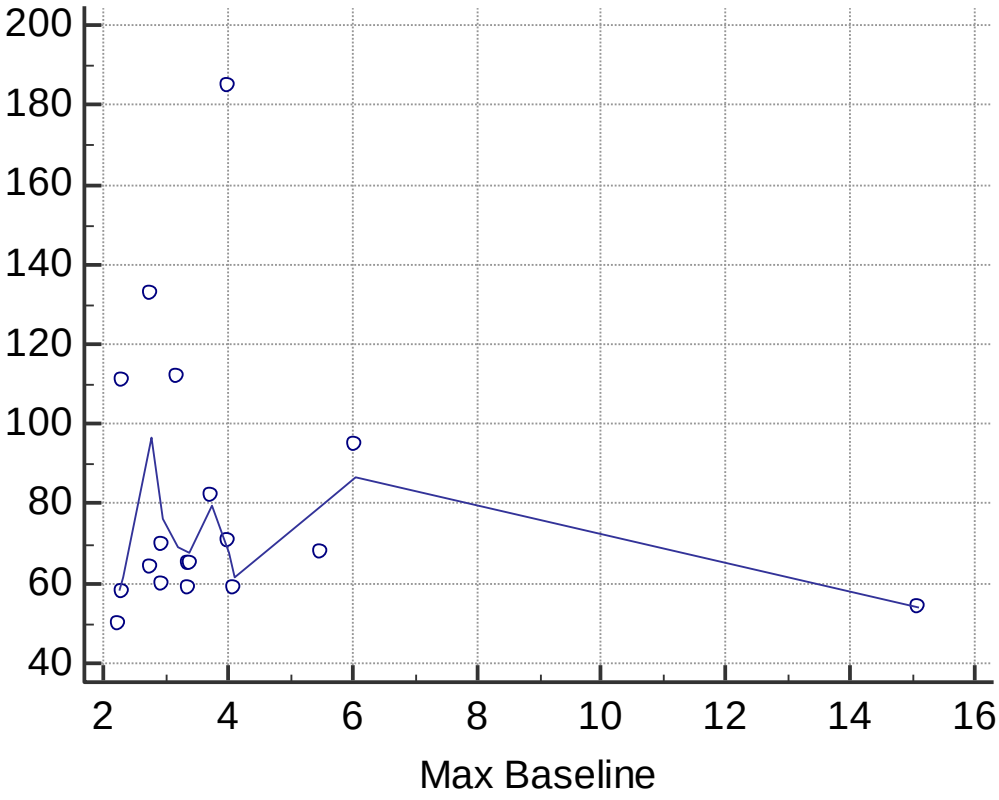

Figure 4-13: AFOS and SUV max at baseline correlation.

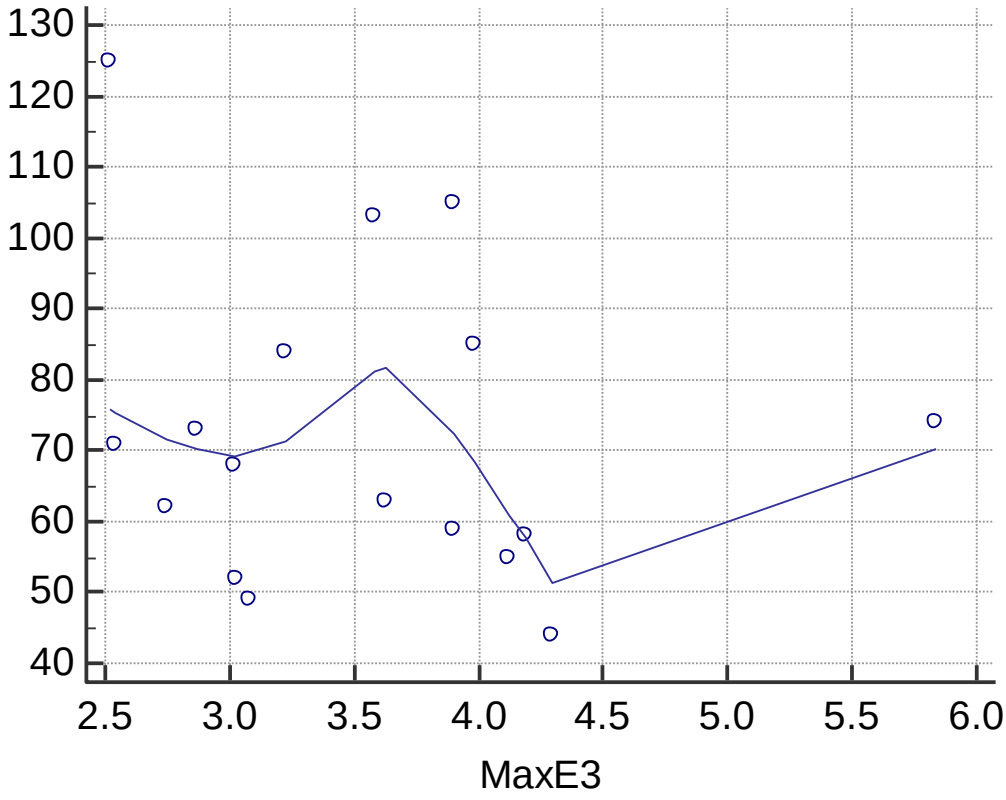

Figure 4-14: AFOS and SUV max one month after chemotherapy correlation.

5 Discussion

The present thesis study is to ascertain if there are changes in F-18 FDG uptake in the liver after chemotherapy R-CHOP on a patient having diffuse large B-cell non-Hodgkin's lymphoma. In our study, liver SUVmean and SUVmax is compared to before chemotherapy with one week after, one month after and four months after chemotherapy. The present study shows that there was no significant change in SUVmax and SUVmean value one week after chemotherapy, but the changes were significant for SUV mean one month and four months after chemotherapy when compared to baseline. The SUVmax and SUVmean values increased during the latter period.

This result partly corroborates with similar studies in this field [25] [48]. A study conducted by Ceriani et al., where 50 patients with DLBCL and treated with R-CHOP6 and R-CHOP demonstrated similar result the study showed a noticeable increase in the mean SUV from basal to interim PET i.e. after 2 cycles of chemotherapy which approximates E4 in the present study, but normalized on final PET scan i.e. 6 cycle of chemotherapy [5]. Ceriani et al. treated their patients with R-MACOP-B/R-VACOP-B and R-CHOP, whereas the patients in our study were treated only with R-CHOP and there was no relation documented that showed an effect in liver was solely due to chemotherapy [25]. A similar study by Chiaravalloti et al. to assess intrapatient liver and mediastinal blood pool 18F-FDG uptake in patients with Hodgkin's lymphoma after ABVD chemotherapy showed similar results to the present study. An increase in SUV mean uptake between PET 0 and PET 2, was seen and the changes seen were significant which approximates E1 and E4 in our study [48].

SUVmax values did not change significantly when compared before and after different cycles of chemotherapy. A similar study by B. Kaya et al demonstrates similar findings where there were some changes between SUV maximum at baseline, interim and final PET but the changes were not significant [25]. Study by Ceriani et al. showed similar finding when compared to basal PET/CT SUV maximum to PET/CT scan 3-4 months after chemotherapy [5]. There was a slight increase in SUV max during this period, but the increase was not significant in our study. Study by Chiaravalloti et al. also showed an increase in SUV max from basal to 2-3 months after ABVD

chemotherapy, however the change seen in the SUV max during that period was significant [48].

Difference in SUV value in different studies were due to different segmentation method. Ceriani et al. used 2-D circular ROI in right lobe of liver, Chiaravalloti used 3-D ROI, whereas in our study manual segmentation was applied for all the slices along volume of the liver. The segmentation method plays a vital factor in obtaining SUVmean and SUVmax value. In our study the baseline SUVmean was 1.95 which almost matched 1.98 in a study by ceriani et al. The interim PET/CT scan after 1 month (SUVmean = 2.108) also closely resembles an interim PET study by Ceriani et al. (SUVmean = 2.17). In case of final PET scan which was done by Ceriani et al. 6-7 month after chemotherapy the SUVmean has decreased to 2. However, in our case the final PET/CT scan was taken 3-4 months after chemotherapy and the SUVmean value was almost similar to previous scan i.e. (2.10 and 2.17). The study could have been more meaningful if the PET/CT scan of the patient could be acquired 6 months and one year after administrating chemotherapy.

Many previous studies have failed to include liver function test and compare the results with the PET/CT scan, which we have been able to include in our study. Alanine aminotransferase value decreased slightly over the period of one month after initiating chemotherapy, whereas the liver SUVmean increased slightly during the same period, both of the changes were insignificant. Abnormal ALT values generally indicate some problem in normal liver functioning. As the change in ALT value was insignificant it is difficult to derive any concrete analysis, and to ascertain the change was due to chemotherapy.

We analyze the correlation of mean and maximum liver standard uptake value with liver function test ALT and AFOS. When mean SUV and ALT is correlated we can see that before chemotherapy, they are weakly related with a correlation coefficient of -0.4875. If we see the correlation coefficient one month after chemotherapy the correlation becomes weaker and almost no correlation exists between mean liver SUV and alanine aminotransferase. In case of maximum liver SUV and alanine aminotransferase weak correlation exists before chemotherapy with -0.3785 and the correlation becomes weaker one month after chemotherapy as illustrated in figure 4-7.

In case of mean liver SUV and alkaline phosphatase positive correlation coefficient changed to negative one month after chemotherapy, i.e. from 0.2170 to -0.2069. However, both the correlation coefficient is weakly related. Similarly, maximum liver SUV and alkaline phosphatase are also weakly related at baseline and one month after chemotherapy with correlation coefficient of -0.1469 and -0-1676 respectively. Alkaline phosphatase a vital parameter for liver function test also decreased from baseline to one month after chemotherapy. The change was considerable, but not significant. ALT and AFOS are a major enzyme present in the

liver and some decrease in levels of both the enzyme has been documented, but a change in insignificant amount limits this study to derive any conclusion.

6 Conclusion

The main purpose of the thesis was to see the change in standard uptake value of liver before and after chemotherapy and compare it to laboratory values concerning liver function test alanine aminotransferase and alkaline phosphatase. The mean standard uptake value did not change for a week after chemotherapy, but scanning after one month and four months of chemotherapy showed significant changes in mean standard uptake value of liver when compared with the baseline. There was a decrease in maximum standard uptake value at baseline and after chemotherapy, but the change was not significant. Mean SUV of liver increased after chemotherapy, whereas alanine aminotransferase and alkaline phosphatase value have both decreased one month after chemotherapy, both the changes were not significant. Maximum SUV, alanine aminotransferase and alkaline phosphatase value decreased one month after chemotherapy, but changes were not significant.

The present study shows that there are changes in mean liver 18F-FDG uptake before and after chemotherapy. However, researchers should be careful as to deriving interpretation of this study and making therapeutic strategies for treatment.

7 Appendix

Mean Liver SUV

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	MeanE1 - MeanE2	-,09027	,23363	,05360	-,20287	,02234	-1,684	18	,109
Pair 2	MeanE1 - MeanE3	-,15463	,21375	,04904	-,25766	-,05161	-3,153	18	,005
Pair 3	MeanE1 - MeanE4	-,21788	,25231	,05788	-,33949	-,09628	-3,764	18	,001
Pair 4	MeanE2 - MeanE3	-,06436	,21930	,05031	-,17006	,04134	-1,279	18	,217
Pair 5	MeanE2 - MeanE4	-,12762	,27600	,06332	-,26064	,00541	-2,015	18	,059
Pair 6	MeanE3 - MeanE4	-,06325	,28155	,06459	-,19896	,07245	-,979	18	,340

Maximum Liver SUV

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	MaxE1 - MaxE2	,62136	3,07252	,70488	-,85954	2,10227	,882	18	,390
Pair 2	MaxE1 - MaxE3	,49363	2,95038	,67686	-,92841	1,91566	,729	18	,475
Pair 3	MaxE1 - MaxE4	,36255	3,03370	,69598	-1,09965	1,82475	,521	18	,609
Pair 4	MaxE2 - MaxE3	-,12774	,84584	,19405	-,53542	,27994	-,658	18	,519
Pair 5	MaxE2 - MaxE4	-,25882	1,00352	,23022	-,74250	,22486	-1,124	18	,276
Pair 6	MaxE3 - MaxE4	-,13108	,72865	,16716	-,48228	,22012	-,784	18	,443

SUV mean and ALT:

Descriptives

			Statistic	Std. Error
MeanBaseline	Mean		1,9541	,10129
	95% Confidence Interval for Mean	Lower Bound	1,7413	
		Upper Bound	2,1669	
	5% Trimmed Mean		1,9283	
	Median		1,9690	
	Variance		,195	
	Std. Deviation		,44153	
	Minimum		1,30	
	Maximum		3,08	

	Range	1,78	
	Interquartile Range	,44	
	Skewness	,795	,524
	Kurtosis	1,129	1,014
MeanInterim	Mean	2,1088	,08355
	95% Confidence Interval for Mean — Lower Bound	1,9332	
	95% Confidence Interval for Mean — Upper Bound	2,2843	
	5% Trimmed Mean	2,0948	
	Median	2,0340	
	Variance	,133	
	Std. Deviation	,36418	
	Minimum	1,51	
	Maximum	2,96	
	Range	1,46	
	Interquartile Range	,44	
	Skewness	,403	,524
	Kurtosis	,253	1,014
ALTBaseline	Mean	2,3632	,27659
	95% Confidence Interval for Mean — Lower Bound	1,7821	
	95% Confidence Interval for Mean — Upper Bound	2,9443	
	5% Trimmed Mean	2,2313	
	Median	2,0000	
	Variance	1,454	
	Std. Deviation	1,20564	
	Minimum	1,30	
	Maximum	5,80	
	Range	4,50	
	Interquartile Range	1,50	
	Skewness	1,570	,524
	Kurtosis	2,391	1,014
ALTInterim	Mean	2,3105	,22333
	95% Confidence Interval for Mean — Lower Bound	1,8413	
	95% Confidence Interval for Mean — Upper Bound	2,7797	
	5% Trimmed Mean	2,2561	
	Median	2,0000	
	Variance	,948	
	Std. Deviation	,97348	

Minimum	1,20	
Maximum	4,40	
Range	3,20	
Interquartile Range	1,10	
Skewness	1,206	,524
Kurtosis	,477	1,014

Paired T test Alanine Aminotransferase at baseline and one month after chemotherapy.

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1 ALT-E1 - ALT-E3	,52632	14,27651	3,27526	-6,35474	7,40737	,161	18	,874

SUV max and ALT

Descriptives

			Statistic	Std. Error
MaxBaseline	Mean		4,0275	,65741
	95% Confidence Interval for Mean	Lower Bound	2,6463	
		Upper Bound	5,4086	
	5% Trimmed Mean		3,5112	
	Median		3,3590	
	Variance		8,212	
	Std. Deviation		2,86559	
	Minimum		2,25	
	Maximum		15,10	
	Range		12,84	
	Interquartile Range		1,26	
	Skewness		3,536	,524
	Kurtosis		13,775	1,014
MaxInterim	Mean		3,5338	,20797
	95% Confidence Interval	Lower Bound	3,0969	

	for Mean	Upper Bound	3,9707	
	5% Trimmed Mean		3,4912	
	Median		3,5810	
	Variance		,822	
	Std. Deviation		,90650	
	Minimum		2,00	
	Maximum		5,84	
	Range		3,84	
	Interquartile Range		1,25	
	Skewness		,679	,524
	Kurtosis		,921	1,014
ALTBaseline	Mean		2,3632	,27659
	95% Confidence Interval for Mean	Lower Bound	1,7821	
		Upper Bound	2,9443	
	5% Trimmed Mean		2,2313	
	Median		2,0000	
	Variance		1,454	
	Std. Deviation		1,20564	
	Minimum		1,30	
	Maximum		5,80	
	Range		4,50	
	Interquartile Range		1,50	
	Skewness		1,570	,524
	Kurtosis		2,391	1,014
ALTInterim	Mean		2,3105	,22333
	95% Confidence Interval for Mean	Lower Bound	1,8413	
		Upper Bound	2,7797	
	5% Trimmed Mean		2,2561	
	Median		2,0000	
	Variance		,948	
	Std. Deviation		,97348	
	Minimum		1,20	
	Maximum		4,40	
	Range		3,20	
	Interquartile Range		1,10	
	Skewness		1,206	,524
	Kurtosis		,477	1,014

Mean liver SUV and AFOS

			Statistic	Std. Error
MeanBaseline	Mean		1,9541	,10129
	95% Confidence Interval for Mean	Lower Bound	1,7413	
		Upper Bound	2,1669	
	5% Trimmed Mean		1,9283	
	Median		1,9690	
	Variance		,195	
	Std. Deviation		,44153	
	Minimum		1,30	
	Maximum		3,08	
	Range		1,78	
	Interquartile Range		,44	
	Skewness		,795	,524
	Kurtosis		1,129	1,014
MeanInterim	Mean		2,1088	,08355
	95% Confidence Interval for Mean	Lower Bound	1,9332	
		Upper Bound	2,2843	
	5% Trimmed Mean		2,0948	
	Median		2,0340	
	Variance		,133	
	Std. Deviation		,36418	
	Minimum		1,51	
	Maximum		2,96	
	Range		1,46	
	Interquartile Range		,44	
	Skewness		,403	,524
	Kurtosis		,253	1,014
AFOSbaseline	Mean		8,0474	,77537
	95% Confidence Interval for Mean	Lower Bound	6,4184	
		Upper Bound	9,6764	
	5% Trimmed Mean		7,6360	
	Median		6,8000	
	Variance		11,423	

	Std. Deviation	3,37974	
	Minimum	5,00	
	Maximum	18,50	
	Range	13,50	
	Interquartile Range	3,60	
	Skewness	2,003	,524
	Kurtosis	4,240	1,014
AFOSinterim	Mean	7,0000	,50245
	95% Confidence Interval for Mean — Lower Bound	5,9444	
	95% Confidence Interval for Mean — Upper Bound	8,0556	
	5% Trimmed Mean	6,8389	
	Median	6,3000	
	Variance	4,797	
	Std. Deviation	2,19013	
	Minimum	4,40	
	Maximum	12,50	
	Range	8,10	
	Interquartile Range	3,20	
	Skewness	1,155	,524
	Kurtosis	,844	1,014

AFOS baseline and one month after chemotherapy

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1 AFOS-E1 - AFOS-E3	10,47368	26,44358	6,06657	-2,27172	23,21908	1,726	18	,101

Maximum liver SUV and AFOS

		Statistic	Std. Error
MaxBaseline	Mean	4,0275	,65741
	95% Confidence Interval for Mean — Lower Bound	2,6463	
	95% Confidence Interval for Mean — Upper Bound	5,4086	
	5% Trimmed Mean	3,5112	
	Median	3,3590	

	Variance		8,212	
	Std. Deviation		2,86559	
	Minimum		2,25	
	Maximum		15,10	
	Range		12,84	
	Interquartile Range		1,26	
	Skewness		3,536	,524
	Kurtosis		13,775	1,014
MaxInterim	Mean		3,5338	,20797
	95% Confidence Interval for Mean	Lower Bound	3,0969	
		Upper Bound	3,9707	
	5% Trimmed Mean		3,4912	
	Median		3,5810	
	Variance		,822	
	Std. Deviation		,90650	
	Minimum		2,00	
	Maximum		5,84	
	Range		3,84	
	Interquartile Range		1,25	
	Skewness		,679	,524
	Kurtosis		,921	1,014
AFOSbaseline	Mean		8,0474	,77537
	95% Confidence Interval for Mean	Lower Bound	6,4184	
		Upper Bound	9,6764	
	5% Trimmed Mean		7,6360	
	Median		6,8000	
	Variance		11,423	
	Std. Deviation		3,37974	
	Minimum		5,00	
	Maximum		18,50	
	Range		13,50	
	Interquartile Range		3,60	
	Skewness		2,003	,524
	Kurtosis		4,240	1,014
AFOSinterim	Mean		7,0000	,50245
	95% Confidence Interval for Mean	Lower Bound	5,9444	
		Upper Bound	8,0556	

	5% Trimmed Mean	6,8389	
	Median	6,3000	
	Variance	4,797	
	Std. Deviation	2,19013	
	Minimum	4,40	
	Maximum	12,50	
	Range	8,10	
	Interquartile Range	3,20	
	Skewness	1,155	,524
	Kurtosis	,844	1,014

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